BMJ Open

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030266
Article Type:	Research
Date Submitted by the Author:	07-Mar-2019
Complete List of Authors:	Shamsrizi, Parichehr; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Gladstone, Beryl Primrose ; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Carrara, Elena; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Luise, Dora; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Cona, Andrea; ASST Santi Paolo e Carlo, Clinic of Infectious and Tropical Diseases, Department of Health Sciences Bovo, Chiara; Integrated University Hospital of Verona, Medical Direction Tacconelli, Evelina; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health
Keywords:	Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

AUTHORS:

Parichehr Shamsrizi[1], Beryl Primrose Gladstone[1], Elena Carrara[2], Dora Luise[2], Andrea Cona[3], Chiara Bovo[4], Evelina Tacconelli[1,2]

AFFILIATIONS:

1) Division of Infectious Disease, Department of Internal Medicine I, DZIF Partner site, Tübingen University Hospital, Tübingen, Germany
2) Division of Infectious Disease, Department of Diagnostic and Public Health, University Hospital of Verona, Verona, Italy
3) Clinic of Infectious and Tropical Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
4) Medical Direction, University Hospital of Verona, Verona, Italy

CORRESPONDING AUTHOR: Elena Carrara, MD

Address: Division of Infectious Disease, Department of Diagnostic and Public Health, University Hospital of Verona, Verona, Italy

Piazzale L.A. Scuro 10, Dipartimento di Malattie Infettive, Policlinico Borgo Roma, 37100 Verona, Italy.

Phone number: +39 3339566252

Email: elena.carrara@univr.it

WORD COUNT: 2372

ABSTRACT

Objective To assess the variation of effect estimates in the analysis of mortality and length of stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae.

Design Systematic review and meta-analysis

Methods Literature search for clinical studies from 1 January 1960 to 1 October 2018 was conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream infections (BSIs) and non-invasive infections. Any change in the effect estimates was assessed by grouping studies according to design, setting, economy-based country classification, reporting period, microbiological aetiology, infection type, and adjustment for appropriateness of empirical treatment. The impact of ESBL production was calculated using random effect meta-analysis and heterogeneity was evaluated by I^2 statistics.

Results Eighty-four studies including 22,030 patients and 149 outcome measures were included in the meta-analysis. Most studies were retrospective cohorts from high-income countries, providing unadjusted estimates. ESBL production in patients with BSIs (56 studies) increased the RR for all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; p<0.001), attributable mortality (16 studies) by 1.75 (95% CI: 1.448-2.108; p<0.001), and WMD in the intensive care unit by 3.07 days (95% CI: 1.61-4.54; p<0.001). WMD in hospital LOS was significantly higher in BSIs (4.41 days; 95% CI: 3.37-5.46; p<0.001) and non-invasive infections (2.19 days; 95% CI: 1.56-2.81; p<0.001). Subgroup analyses showed variation of estimates by study design, population, strain, and assessment of appropriateness of empiric treatment. High heterogeneity was observed in all analyses.

Conclusions Current evidence of the clinical burden of infections caused by ESBL-producing bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from retrospective studies. Despite these limitations, ESBL production in strains causing BSIs seems associated with higher all-cause and attributable mortality and longer hospitalisation.

KEYWORDS

Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Evidence of the impact of ESBL production on mortality and length of stay in strains causing invasive and non-invasive infections was collected systematically.
- Effect of multiple epidemiological and clinical variables was assessed in the calculation of estimates.
- Heterogeneity among studies was assessed.
- Only few studies had been performed in high-risk populations or low-income countries.

INTRODUCTION

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are responsible for high morbidity and mortality worldwide.[1,2,3] The 2018 World Health Organization list of antibiotic-resistant pathogens identified mortality as the most important criteria to prioritise bacteria for research and development of new, effective antibiotics.[1] In this prioritisation exercise, ESBL-producing Enterobacteriaceae were designated a critical priority because of their high all-cause mortality and high prevalence globally in healthcare-associated and community-acquired infections. The incidence and attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing Enterobacteriaceae, in European countries has been recently estimated using a modelling analysis.[4] In 2015 ESBL-producing *Escherichia coli* was responsible for almost 300,000 infections in Europe and 9,000 attributable deaths, and ESBL-producing *Klebsiella pneumoniae* caused around 70,000 infections and more than 3,500 deaths. The major limitation of this analysis is the sparseness of evidence on mortality due to ESBL-producing bacteria, which was limited largely to studies conducted in high-income countries.

Two systematic reviews have been performed to define the impact of ESBL production on mortality due to Enterobacteriaceae.[2,3] Both meta-analyses included studies targeting bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated bacteraemia compared to non-ESBL Enterobacteriaceae bacteraemia. A major drawback of the analyses, highlighted by the authors, was the lack of control for confounding and limited adjustment for empiric therapy. No systematic review has been performed to assess attributable mortality and other indicators of clinical impact such as length of stay (LOS).

Because estimates of clinical burden drive policy design for antibiotic stewardship and infection control interventions, precise and current estimates are essential. The objective of this systematic review and meta-analysis was to assess the variation of effect estimates in the analysis of mortality and LOS in patients with infections due to ESBL-producing Enterobacteriaceae.

METHODS

Literature search strategy

The search was performed by 2 researchers (BPG and PS) in PubMed on 05 October 2018 using the following search string: (ESBL AND Escherichia coli AND mortality" OR "ESBL AND Klebsiella pneumoniae AND mortality) OR (ESBL AND Escherichia coli AND length

of stay OR length of hospitalisation) OR (ESBL AND Klebsiella pneumoniae AND length of stay OR length of hospitalisation). Reference lists of retrieved articles were also searched.

Eligibility criteria

We included all clinical studies with a comparison group assessing all-cause mortality, attributable mortality, and overall LOS and intensive care unit stay (ICU) LOS in hospitalised patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018 irrespective of the clinical setting and study design were included. The search was restricted to English language publications. Diagnostic studies, reviews, case reports, non-clinical studies, and abstracts of conference presentations were not included.

Data extraction

Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted data. In case of disagreement, a third reviewer (DL) was consulted. Extracted data were collected in an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of publication, year of study, time of data collection, study design, comparison group, study setting, population, aetiology, type and site of infection, and raw data related to mortality and LOS/ICU-LOS. Countries were classified as high-, middle-, or low-income using the World Bank Atlas method.[5] Adjusted effect estimates such as odds ratios (ORs) or hazard ratios and quality indicators such as reporting of antibiotic therapy, appropriateness of empirical treatment, resistance mechanisms, and minimum inhibitory concentrations (MICs) were also extracted.

Mortality data were extracted as all-cause mortality or attributable mortality as defined in the studies. Where available, prespecified time periods for mortality assessment (i.e., 14 days, 28 days, in-hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean and standard deviation or median and interquartile range.

Data analysis

The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in patients with ESBL infections compared with those in patients with non-ESBL infections and, where available, with uninfected patients. The impact of ESBL production on attributable and all-cause mortality was calculated with random effect meta-analysis and expressed as RR with 95% confidence interval (CI). WMD in days with 95% CI was calculated to express the excess in LOS and ICU-LOS. Analysis of mortality focused on BSIs while LOS was

determined for BSIs and non-invasive infections (i.e., urinary tract infections, respiratory tract infections, surgical site infection).

Variation of the effect estimate was assessed by grouping the studies according to the following confounders: mortality time assessment (7 vs 14 days), aetiology (*E. coli* vs *K. pneumoniae*), clinical setting (paediatric, oncology, ICU), economic country areas (high-income countries [HICs] vs low- and medium-income countries [LMICs]), study design, assessment of empiric therapy, and year. Subgroup analysis was computed only if more than 2 studies were available for each group. Heterogeneity was evaluated by using I^2 statistics. Overall significance testing was carried out using Wald tests adjusted using the Bonferroni correction. The unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment. Reporting and publication bias was presented in funnel plots (supplementary and tested by Egger's test. Statistical analyses were performed using Stata version 15. All meta-analyses were performed in accordance with the Cochrane Collaboration recommendations[6] and reported according to the PRISMA statement.[7]

The protocol is available online .

(https://im1-tuebingen.de/wp content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf)

Patient and Public Involvement

There was no patient or public involvement in this systematic review of published literature.

RESULTS

Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an evidence base of 87 studies (Figure 1).[8-94] The 87 studies included in the qualitative analysis were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies), Thailand (7), USA (7), Taiwan (7), and Spain (7). Sixty (68.9%) studies were performed in HICs, 26 (29.9%) in LMICs, and 1 included both HICs and LMICs.[54] About half (44, 50.6%) were retrospective cohort studies, 24 (27.6%) case cohort studies, and 18 (20.7%) prospective cohort studies; 1 study had an interventional design.[55] The comparison group was patients with infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-infected patients in 2 (2.3%), and both control groups in 3 (3.5%). Most (57, 65.5%) studies included data from the entire hospital, while a few focused on specific settings, mainly ICUs (9, 10.3%) and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were

E. coli (23, 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is provided in online supplementary table S1.

Because data in 3 studies [20,59,85] were insufficient for quantitative analysis, 84 (96.6%) studies were included in the meta-analysis analysing data from 22,030 patients and 149 outcome measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study characteristics for all studies are provided in online supplementary table S2.

All-cause mortality

All-cause mortality was reported in 81 studies including 21,942 patients. ESBL production in patients with BSIs increased all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; p<0.001; I^2=45.3%). The RR increased over time from 1.56 (95% CI: 1.15-2.11; p=0.004) in 1991-1999 to 1.74 (95% CI: 1.50-2.01; p<0.001) in 2000-2009, and it was stable in 2010-2018 (1.72, 95% CI: 1.39-2.13; p<0.001). The RR was higher in studies assessing appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; p<0.001) than in those that did not (RR=1.55; 95% CI 1.26-1.90; p<0.001). The subgroup analysis by pathogen showed that ESBL production increased the RR in BSIs due to *E. coli* (RR=1.82; 95% CI: 1.50-2.21; p<0.001) compared to those due to *K. pneumoniae* (RR=1.48; 95% CI: 1.17-1.87; p=0.001). Stratification by population age showed an higher RR in paediatric population (RR=2.09; 95% CI: 1.62-2.71; p<0.001). Effect estimates did not vary significantly by study country, mortality time assessment (14 vs 28 days), ESBL molecular resistance mechanisms, or study design (Figure 2 and online supplementary figure S1). Adjusted estimates for inappropriate empirical antibiotic therapy were provided for 14 studies. The pooled unadjusted OR for all-cause mortality was 2.91 (95% CI: 2.23-3.81; p<0.001, I^2=27.1%; p=0.164) and the pooled OR after adjusting for receipt of appropriate empirical treatment was 3.22 (95% CI: 1.53-6.76; p=0.002; I^2=87.5%; p<0.001).

Attributable mortality

Attributable mortality was analysed in 16 studies including 2,885 patients. All studies were performed in HICs. ESBL production in patients with BSIs increased the risk of attributable mortality by a factor of 1.75 (95% CI: 1.45-2.11; p<0.001; I^2=0%). The RR increased over time from 1.53 (95% CI: 1.10-2.12; p=0.011) in 1991-1999 to 1.91 (95% CI: 1.43-2.54; p<0.001) in 2000-2009 (Figure 3). Pathogen-specific RR for attributable mortality was 1.60 (95% CI: 1.18-2.15; p=0.002) for *K. pneumoniae* and 1.76 (95% CI: 1.33-2.34; p<0.001) when the gram-negative organisms were analysed all together without species differentiation.

The subgroup analysis showed the RR was lower in case cohort studies (1.56; 95% CI: 1.09-2.25; p=0.016) than in cohort studies (1.80; 95% CI: 1.37-2.37; p<0.001).

Length of stay

LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive infections) analysing 38 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95% CI: 3.37-5.46; p<0.001) and decreased from 5.72 days (95% CI: 2.69-8.75; p<0.001) in 1991-1999 to 4.22 days (95% CI: 3.02-5.43; p<0.001) in 2000-2009 and was stable up to 2018 (4.30 days; 95% CI: 1.38-7.22; p=0,004). Higher WMD (p<0.001) was observed for BSIs due to *K. pneumoniae* (7.67 days; 4.63-10.71) than for those due to *E. coli* (6.07 days; 95% CI 3.71-8.43). Retrospective cohort studies reported higher (p<0.001) WMD (6.43 days; 95% CI: 4.66-8.21; p<0.001) than case cohort studies (3.32 days; 95% CI: 2.03-4.61). Studies in HICs showed higher WMD (4.56 days; 95% CI 3.43-5.70; p<0.001) than studies in LMICs (3.55 days; 95% CI 0.84-6.26; p=0.01) (Figure 4).

Studies with non-invasive infections reported a WMD of 2.19 days (95% CI: 1.56-2.81; p<0.001), which decreased from 7.66 (95% CI: 5.83-9.46; p<0.001) in 2000-2009 to 1.44 (95% CI: 0.77-2.10; p<0.001) in 2010-2018 (online supplementary figure S3).

The data on ICU-LOS were provided in 7 studies and showed that BSIs caused by ESBL producers had a WMD of LOS of 3.07 days (95% CI: 1.61-4.54; p<0.001).

Egger's test and the funnel plots (online supplementary figure S4 and S5) showed evidence for small study effects (p<0.001) and publication bias.

DISCUSSION

This systematic review shows that ESBL production has a significant impact on the most relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality, attributable mortality, and LOS both in hospital and in ICU were higher for patients with BSIs due to ESBL-producing Enterobacteriaceae than for patients with BSIs due to non-ESBL-producing strains. Non-invasive infections caused by ESBL-producing strains were associated with prolonged LOS. Within the limitation of the low number of studies evaluating specific patient populations, paediatric and cancer patients seemed to suffer a higher impact of ESBL invasive infections than the overall population. Stratifying by pathogen type, the impact of ESBL production was higher for *E. coli* BSIs than for *K. pneumoniae* BSIs. No relevant differences in mortality analysis emerged with stratification by study design or country income level. Impact of ESBL infections on mortality became more evident in more recent

studies. Studies reporting on appropriateness of empirical therapy, ESBL resistance mechanisms, and MICs showed a higher clinical impact of ESBL infections than studies not assessing these variables. In particular, pooled ORs adjusted for inappropriate empirical treatment, showed a remarkably higher OR for mortality in patients with ESBL infections.

Our findings confirm the results of previous systematic reviews. Schwaber et al. performed a systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies published through 2003.[2] The authors show a pooled RR for all-cause mortality of 1.85 but, in contrast to our study, they combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in the analysis because of sample size limitations. Rottier et al. analysed studies published through 2010 and adjusting results for inappropriate empirical treatment found an adjusted OR of 1.37.[3] Our study, adding more than 50 studies in 17 years to the Rottier systematic review, confirmed the clinical importance of ESBL production to all-cause mortality and for the first time assessed the role of ESBL production on attributable mortality. We addressed relevant confounders through subgroup analyses and found that population, pathogen, and assessment of empiric therapy all had an impact on estimates. Because we believe that appropriate empirical treatment plays a relevant role in invasive infections, we performed a secondary analysis by pooling only adjusted ORs and confirming the significant impact of antibiotic resistance as already shown in a previously published systematic review.[95] The impact of ESBL production on LOS has been also estimated, assessing BSIs and non-invasive infections separately and confirming the prolongation of hospitalisation.

Our study has some limitations. Although results of the meta-analyses were significant in all the subgroups, we could analyse only a limited number of studies providing information for subgroups such as haematological patients and low-income countries, making generalizability of results less certain for these specific patient populations. Only a few studies reported MIC data or specific ESBL molecular resistant phenotype (i.e., AmpC). Moreover, publication bias was detected in both the main analyses (all-cause mortality and LOS), thus implying the possibility that results from small studies with non-significant results might have been conducted and not published, resulting in a possible overestimation of our results. The non-homogeneous reporting of some relevant data in published literature (e.g., disease severity and underlying comorbidities) may also have affected the precision of the estimate. Patients with ESBL are intrinsically at higher risk of mortality and complications because they are often older, have more comorbidities or higher antibiotic exposure, and are at higher risk of receiving inappropriate empirical treatment.[96]

In summary, our systematic review emphasises the importance of suspicion and confirmation of ESBL production as soon as possible for invasive infections and demonstrates that ESBL production increases the risk of attributable mortality and LOS in both hospital and ICU for invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of mortality and prolonged LOS even after adjustment for empiric inappropriate treatment. Control for other relevant confounders is hindered by the sparseness of published data. Future studies addressing the clinical burden of drug-resistant infections must include ESBL production and should assess both the impact of molecular mechanisms of resistance and effect on specific patient populations such as haematological patients and those in LMIC.

Acknowledgements We thank Anne McDonough, a professional medical writer who provided medical writing support funded by the authors.

Author Contributions ET contributed to the study concept. BPG and PS performed data analysis. PS and AC extracted data and wrote the first draft of the manuscript. DL contributed to the first draft of the manuscript. EC and ET wrote the final version of the manuscript. CB reviewed the paper. All authors read, edited, and approved the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding This work was supported by the German Center for Infection Research Clinical Research Unit for Health-Care Associated Infections grant number TTU 08.701 and DRIVE-AB (115618). The funder had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Competing interests The authors report no competing interests.

Patient consent Not required

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Requests for data should be addressed to the corresponding author.

REFERENCES

1. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 2018;18:318–27.
2. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:913–20.
3. Rottier WC, Ammerlaan HS, Bonten MJ. Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. *J Antimicrob Chemother* 2012;67:1311–20.
4. Cassini A, Högberg LD, Plachouras D, et al; Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;19:56–66.
5. The World Bank. What is the World Bank Atlas method? https://datahelpdesk.worldbank.org/knowledgebase/articles/77933-what-is-the-world-bank-atlas-method. Accessed January 14, 2019.
6. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
7. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
8. Lautenbach E, Patel JB, Bilker WB, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *Clin Infect Dis* 2001;32:1162–71.
9. Leistner R, Sakellariou C, Gurntke S, et al. Mortality and molecular epidemiology associated with extended-spectrum beta-lactamase production in Escherichia coli from bloodstream infection. *Infect Drug Resist* 2014;7:57–62.
10. Lin JN, Chen YH, Chang LL, et al. Clinical characteristics and outcomes of patients with extended-spectrum beta-lactamase-producing bacteremias in the emergency department. *Intern Emerg Med* 2011;6:547–55.

11. Kim HJ, Park JH, Park DI, et al. Clinical impact of extended-spectrum beta-lactamase-producing Enterobacteriaceae in patients with biliary tract infection. *Dig Dis Sci* 2013;58:841–9.
12. Kim SH, Kwon JC, Choi SM, et al. Escherichia coli and Klebsiella pneumoniae bacteremia in patients with neutropenic fever: factors associated with extended-spectrum beta-lactamase production and its impact on outcome. *Ann Hematol* 2013;92:533–41.
13. Pillay T, Pillay DG, Adhikari M, et al. Piperacillin/tazobactam in the treatment of Klebsiella pneumoniae infections in neonates. *Am J Perinatol* 1998;15:47–51.
14. Kim BN, Woo JH, Kim MN, et al. Clinical implications of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae bacteraemia. *J Hosp Infect* 2002;52:99–106.
15. Kim YK, Pai H, Lee HJ, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in children: epidemiology and clinical outcome. *Antimicrob Agents Chemother* 2002;46:1481–91.
16. Bhavnani SM, Ambrose PG, Craig WA, et al. Outcomes evaluation of patients with ESBL- and non-ESBL-producing Escherichia coli and Klebsiella species as defined by CLSI reference methods: report from the SENTRY Antimicrobial Surveillance Program. *Diagn Microbiol Infect Dis* 2006;54:231–6.
17. Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol* 2005;43:745–9.
18. Panhotra BR, Saxena AK, Al-Ghamdi AM. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae hospital acquired bacteremia. Risk factors and clinical outcome. *Saudi Med J* 2004;25:1871–6.
19. Marra AR, Wey SB, Castelo A, et al. Nosocomial bloodstream infections caused by Klebsiella pneumoniae: impact of extended-spectrum beta-lactamase (ESBL) production on clinical outcome in a hospital with high ESBL prevalence. *BMC Infect Dis* 2006;6:24.
20. Skippen I, Shemko M, Turton J, et al. Epidemiology of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp.: a nested case-control study from a tertiary hospital in London. *J Hosp Infect* 2006;64:115–23.
21. Schwaber MJ, Navon-Venezia S, Kaye KS, et al. Clinical and economic impact of bacteremia with extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2006;50:1257–62.

22. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Clinical and molecular epidemiology of community-onset, extended-spectrum beta-lactamase-producing Escherichia coli infections in Thailand: a case-case-control study. *Am J Infect Control* 2007;35:606–12.
23. Tumbarello M, Spanu T, Sanguinetti M, et al. Bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae: risk factors, molecular epidemiology, and clinical outcome. *Antimicrob Agents Chemother* 2006;50:498–504.
24. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Risk factors for and outcomes of healthcare-associated infection due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae in Thailand. *Infect Control Hosp Epidemiol* 2007;28:873–6. doi: 10.1086/518725
25. Kanafani ZA, Mehio-Sibai A, Araj GF, et al. Epidemiology and risk factors for extended-spectrum beta-lactamase-producing organisms: a case control study at a tertiary care center in Lebanon. *Am J Infect Control* 2005;33:326–32.
26. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in children. *Pediatrics* 2005;115:942–9.
27. Loh LC, Nor Izran Hanim Bt Abdul S, Rosdara Masayuni Bt Mohd S, et al. Hospital Outcomes of Adult Respiratory Tract Infections with Extended-Spectrum B-Lactamase (ESBL) Producing Klebsiella Pneumoniae. *Malays J Med Sci* 2007;14:36–40.
28. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing E. coli compared to non-ESBL producing E. coli. *J Infect* 2007;55:254–9. doi: 10.1016/j.jinf.2007.04.007
29. Song KH, Jeon JH, Park WB, et al. Clinical outcomes of spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species: a retrospective matched case-control study. *BMC Infect Dis* 2009;9:41.
30. Bennett JW, Robertson JL, Hospenthal DR, et al. Impact of extended spectrum beta-lactamase producing Klebsiella pneumoniae infections in severely burned patients. *J Am Coll Surg* 2010;211:391–9.
31. Trecarichi EM, Tumbarello M, Spanu T, et al. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by Escherichia coli in patients with hematological malignancies. *J Infect* 2009;58:299–307.
32. Tuon FF, Kruger M, Terreri M, et al. Klebsiella ESBL bacteremia-mortality and risk factors. *Braz J Infect Dis* 2011;15:594–8.

33. Kang CI, Song JH, Chung DR, et al. Risk factors and treatment outcomes of community-onset bacteraemia caused by extended-spectrum beta-lactamase-producing Escherichia coli. *Int J Antimicrob Agents* 2010;36:284–7.
34. Pena C, Gudiol C, Calatayud L, et al. Infections due to Escherichia coli producing extended-spectrum beta-lactamase among hospitalised patients: factors influencing mortality. *J Hosp Infect* 2008;68:116–22.
35. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. *Antimicrob Agents Chemother* 2010;54:4085–91.
36. Kang CI, Chung DR, Ko KS, et al. Risk factors for infection and treatment outcome of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in patients with hematologic malignancy. *Ann Hematol* 2012;91:115–21.
37. Wu YH, Chen PL, Hung YP, et al. Risk factors and clinical impact of levofloxacin or cefazolin nonsusceptibility or ESBL production among uropathogens in adults with community-onset urinary tract infections. *J Microbiol Immunol Infect* 2014;47:197–203.
38. Rodriguez-Bano J, Picon E, Gijon P, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli: risk factors and prognosis. *Clin Infect Dis* 2010;50:40–8.
39. Gurntke S, Kohler C, Steinmetz I, et al. Molecular epidemiology of extended-spectrum beta-lactamase (ESBL)-positive Klebsiella pneumoniae from bloodstream infections and risk factors for mortality. *J Infect Chemother* 2014;20:817–9.
40. Oh MM, Chae JY, Kim JW, et al. Positive culture for extended-spectrum beta-lactamase during acute prostatitis after prostate biopsy is a risk factor for progression to chronic prostatitis. *Urology* 2013;81:1209–12.
41. Leistner R, Gurntke S, Sakellariou C, et al. Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive K. pneumoniae and E. coli: an analysis of the disease burden in a large cohort. *Infection* 2014;42:991–7.
42. Ku NS, Chung HS, Choi JY, et al. Clinical usefulness of the 2010 clinical and laboratory standards institute revised breakpoints for cephalosporin use in the treatment of bacteremia caused by Escherichia coli or Klebsiella spp. *Biomed Res Int* 2015;2015:831074.
43. Anunnatsiri S, Towiwat P, Chaimanee P. Risk factors and clinical outcomes of extended spectrum beta-lactamase (ESBL)-producing Escherichia coli septicemia at Srinagarind

University Hospital, Thailand. *Southeast Asian J Trop Med Public Health* 2012;43:1169–77.

44. Kang CI, Kim SH, Kim DM, et al. Risk factors for and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae. *Infect Control Hosp Epidemiol* 2004;25:860–7.
45. Raviv Y, Shitrit D, Amital A, et al. Multidrug-resistant Klebsiella pneumoniae acquisition in lung transplant recipients. *Clin Transplant* 2012;26:E388–94.
46. MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. *J Hosp Med* 2014;9:232–8.
47. Abhilash KP, Veeraraghavan B, Abraham OC. Epidemiology and outcome of bacteremia caused by extended spectrum beta-lactamase (ESBL)-producing Escherichia coli and Klebsiella spp. in a tertiary care teaching hospital in south India. *J Assoc Physicians India* 2010;58 Suppl:13-7.
48. Shanthi M, Sekar U. Extended spectrum beta lactamase producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *J Assoc Physicians India* 2010;58 Suppl:41–4.
49. Han SB, Jung SW, Bae EY, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in febrile neutropenic children. *Microb Drug Resist* 2015;21:244–51.
50. Lee S, Song DY, Cho SH, et al. Impact of extended-spectrum beta-lactamase on acute pyelonephritis treated with empirical ceftriaxone. *Microb Drug Resist* 2014;20:39–44.
51. Chayakulkeeree M, Junsriwong P, Keerasuntonpong A, et al. Epidemiology of extended-spectrum beta-lactamase producing gram-negative bacilli at Siriraj Hospital, Thailand, 2003. *Southeast Asian J Trop Med Public Health* 2005;36:1503–9.
52. Apisarnthanarak A, Kiratisin P, Mundy LM. Predictors of mortality from community-onset bloodstream infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. *Infect Control Hosp Epidemiol* 2008;29:671–4.
53. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Predictors of mortality among patients with community-onset infection due to extended-spectrum beta-lactamase-producing Escherichia coli in Thailand. *Infect Control Hosp Epidemiol* 2008;29:80–2.

54. Jean SS, Ko WC, Xie Y, et al. Clinical characteristics of patients with community-acquired complicated intra-abdominal infections: a prospective, multicentre, observational study. *Int J Antimicrob Agents* 2014;44:222–8.
55. Lee J, Pai H, Kim YK, et al. Control of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a children's hospital by changing antimicrobial agent usage policy. *J Antimicrob Chemother* 2007;60:629–37.
56. Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, et al. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. *Int J Clin Pract* 2012;66:891–6.
57. Ha YE, Kang CI, Cha MK, et al. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in patients with cancer. *Int J Antimicrob Agents* 2013;42:403–9.
58. Du B, Long Y, Liu H, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bloodstream infection: risk factors and clinical outcome. *Intensive Care Med* 2002;28:1718–23.
59. Stone PW, Gupta A, Loughrey M, et al. Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae outbreak in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2003;24:601–6.
60. Pena C, Pujol M, Ardanuy C, et al. An outbreak of hospital-acquired Klebsiella pneumoniae bacteraemia, including strains producing extended-spectrum beta-lactamase. *J Hosp Infect* 2001;47:53–9.
61. Kola A, Maciejewski O, Sohr D, et al. Clinical impact of infections caused by ESBL-producing E. coli and K. pneumoniae. *Scand J Infect Dis* 2007;39:975–82.
62. Tsai MH, Lee IT, Chu SM, et al. Clinical and Molecular Characteristics of Neonatal Extended-Spectrum beta-Lactamase-Producing Gram-Negative Bacteremia: A 12-Year Case-Control-Control Study of a Referral Center in Taiwan. *PLoS One* 2016;11(8):e0159744.
63. Maslikowska JA, Walker SA, Elligsen M, et al. Impact of infection with extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella species on outcome and hospitalization costs. *J Hosp Infect* 2016;92:33–41.
64. Onken A, Said AK, Jorstad M, et al. Prevalence and antimicrobial resistance of microbes causing bloodstream infections in Unguja, Zanzibar. *PLoS One* 2015;10:e0145632.
65. Nguyen ML, Toye B, Kanji S, et al. Risk factors for and outcomes of bacteremia caused by extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella species at a

Canadian tertiary care hospital. *Can J Hosp Pharm* 2015;68(2):136–43. [published Online First: 2015/05/13]

66. Denis B, Lafaurie M, Donay JL, et al. Prevalence, risk factors, and impact on clinical outcome of extended-spectrum beta-lactamase-producing Escherichia coli bacteraemia: a five-year study. Int *J Infect Dis* 2015;39:1–6.
67. Chopra T, Marchaim D, Johnson PC, et al. Risk factors for bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: A focus on antimicrobials including cefepime. *Am J Infect Control* 2015;43:719–23.
68. Artero A, Esparcia A, Alberola J, et al. Prospective cohort study of risk factors for extended-spectrum ss-lactamase-producing Escherichia coli urinary tract infections in elderly patients admitted to hospital. *Int J Clin Pract* 2017;71:doi:10.1111/ijcp.13001
69. Chen IL, Huang HC, Wu CT, et al. Analysis of early-onset bloodstream infection due to Escherichia coli infection in premature babies. *Medicine* 2017;96:e7748.
70. Islas-Munoz B, Volkow-Fernandez P, Ibanes-Gutierrez C, et al. Bloodstream infections in cancer patients. Risk factors associated with mortality. *Int J Infect Dis* 2018;71:59–64.
71. Ma J, Li N, Liu Y, et al. Antimicrobial resistance patterns, clinical features, and risk factors for septic shock and death of nosocomial E coli bacteremia in adult patients with hematological disease: A monocenter retrospective study in China. *Medicine* 2017;96:e6959.
72. Man MY, Shum HP, Chan YH, et al. Clinical predictors and outcomes of Klebsiella pneumoniae bacteraemia in a regional hospital in Hong Kong. *J Hosp Infect* 2017;97:35–41.
73. Marando R, Seni J, Mirambo MM, et al. Predictors of the extended-spectrum-beta lactamases producing Enterobacteriaceae neonatal sepsis at a tertiary hospital, Tanzania. *Int J Med Microbiol* 2018;308:803–11.
74. Namikawa H, Yamada K, Fujimoto H, et al. Clinical characteristics of bacteremia caused by extended-spectrum beta-lactamase-producing Escherichia coli at a tertiary hospital. *Intern Med* 2017;56:1807–15.
75. Shi SH, Feng XN, Lai MC, et al. Biliary diseases as main causes of pyogenic liver abscess caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Liver Int* 2017;37:727–34.

76. Tanir Basaranoglu S, Ozsurekci Y, Aykac K, et al. A comparison of blood stream infections with extended spectrum beta-lactamase-producing and non-producing Klebsiella pneumoniae in pediatric patients. *Ital J Pediat* 2017;43:79.
77. Razazi K, Mekontso Dessap A, Carteaux G, et al. Frequency, associated factors and outcome of multi-drug-resistant intensive care unit-acquired pneumonia among patients colonized with extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Ann Intensive Care* 2017;7:61.
78. Ray S, Anand D, Purwar S, et al. Association of high mortality with extended-spectrum beta-lactamase (ESBL) positive cultures in community acquired infections. *J Crit Care* 2018;44:255–60.
79. Haruki Y, Hagiya H, Haruki M, et al. Clinical characteristics and outcome of critically ill patients with bacteremia caused by extended-spectrum beta-lactamase-producing and non-producing Escherichia coli. *J Infect Chemother* 2018;24:944–7.
80. Lin WT, Tang HJ, Lai CC, et al. Clinical manifestations and bacteriological features of culture-proven Gram-negative bacterial arthritis. *J Microbiol Immunol Infect* 2017;50:527–31.
81. Buys H, Muloiwa R, Bamford C, et al. Klebsiella pneumoniae bloodstream infections at a South African children's hospital 2006-2011, a cross-sectional study. BMC Infect Dis 2016;16:570.
82. Lee CC, Lee CH, Hong MY, et al. Propensity-matched analysis of the impact of extended-spectrum beta-lactamase production on adults with community-onset Escherichia coli, Klebsiella species, and Proteus mirabilis bacteremia. *J Microbiol Immunol Infect* 2018;51:519–26.
83. Huang YY, Alleyne A, Leung V, et al. Urosepsis due to extended-ppectrum beta-lactamase-producing Escherichia coli: a retrospective, single-centre review of risk Factors and clinical outcomes. *Can J Hosp Pharm* 2018;71:119-27.
84. Komatsu Y, Kasahara K, Inoue T, et al. Molecular epidemiology and clinical features of extended-spectrum beta-lactamase- or carbapenemase-producing Escherichia coli bacteremia in Japan. *PLoS One* 2018;13:e0202276.
85. Liu M, Li M, Wu L, et al. Extended-spectrum beta-lactamase-producing E. coli septicemia among rectal carriers in the ICU. *Medicine* 2018;97:e12445.
86. Nivesvivat T, Piyaraj P, Thunyaharn S, et al. Clinical epidemiology, risk factors and treatment outcomes of extended-spectrum beta-lactamase producing Enterobacteriaceae

bacteremia among children in a tertiary care hospital, Bangkok, Thailand. *BMC Res Notes* 2018;11:624.

87. Cordery RJ, Roberts CH, Cooper SJ, et al. Evaluation of risk factors for the acquisition of bloodstream infections with extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in the intensive care unit; antibiotic management and clinical outcome. *J Hosp Infect* 2008;68:108–15.
88. Daikos GL, Kosmidis C, Tassios PT, et al. Enterobacteriaceae bloodstream infections: presence of integrons, risk factors, and outcome. *Antimicrob Agents Chemother* 2007;51:2366–72. doi: 10.1128/AAC.00044-07 [published Online First: 2007/04/25]
89. Gudiol C, Calatayud L, Garcia-Vidal C, et al. Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. *J Antimicrob Chemother* 2010;65(2):333–41.
90. Marchaim D, Gottesman T, Schwartz O, et al. National multicenter study of predictors and outcomes of bacteremia upon hospital admission caused by Enterobacteriaceae producing extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2010;54:5099–104.
91. Menashe G, Borer A, Yagupsky P, et al. Clinical significance and impact on mortality of extended-spectrum beta lactamase-producing Enterobacteriaceae isolates in nosocomial bacteremia. *Scand J Infect Dis* 2001;33:188–93.
92. Ortega M, Marco F, Soriano A, et al. Analysis of 4758 Escherichia coli bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. *J Antimicrob Chemother* 2009;63:568–74.
93. Szilagyi E, Fuzi M, Borocz K, et al. Risk factors and outcomes for bloodstream infections with extended-spectrum beta-lactamase-producing Klebsiella pneumoniae ; Findings of the nosocomial surveillance system in Hungary. *Acta Microbiol Immunol Hung* 2009;56:251–62. doi:
94. Tsai SS, Huang JC, Chen ST, et al. Characteristics of Klebsiella pneumoniae bacteremia in community-acquired and nosocomial infections in diabetic patients. *Chang Gung Med J* 2010;33:532–9.
95. Carrara E, Pfeffer I, Zusman O, et al. Determinants of inappropriate empirical antibiotic treatment: systematic review and meta-analysis. *Int J Antimicrob Agents* 2018;51:548–53,
96. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clin Microbiol Infect* 2014;20:973–80.

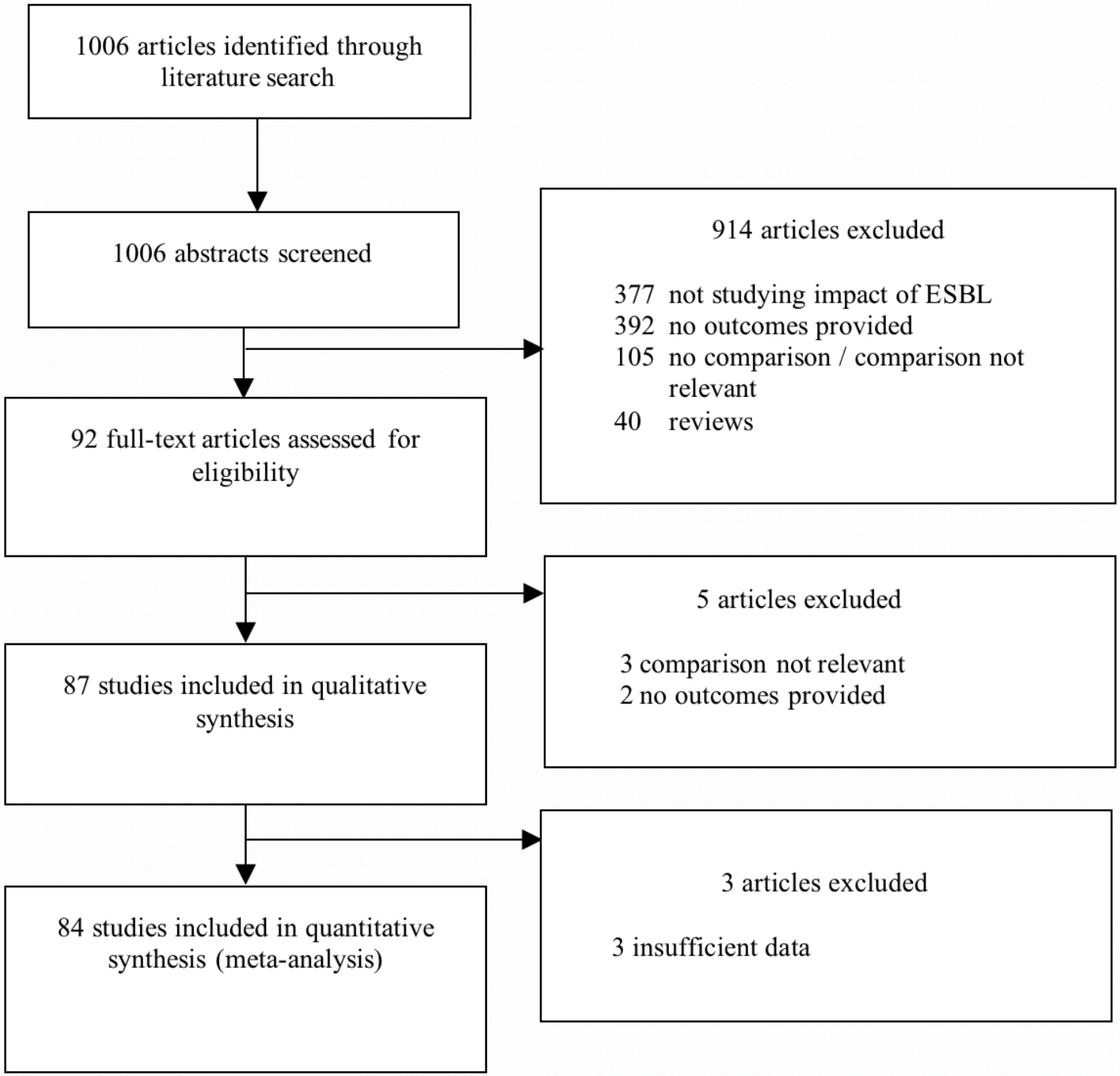
FIGURE LEGENDS

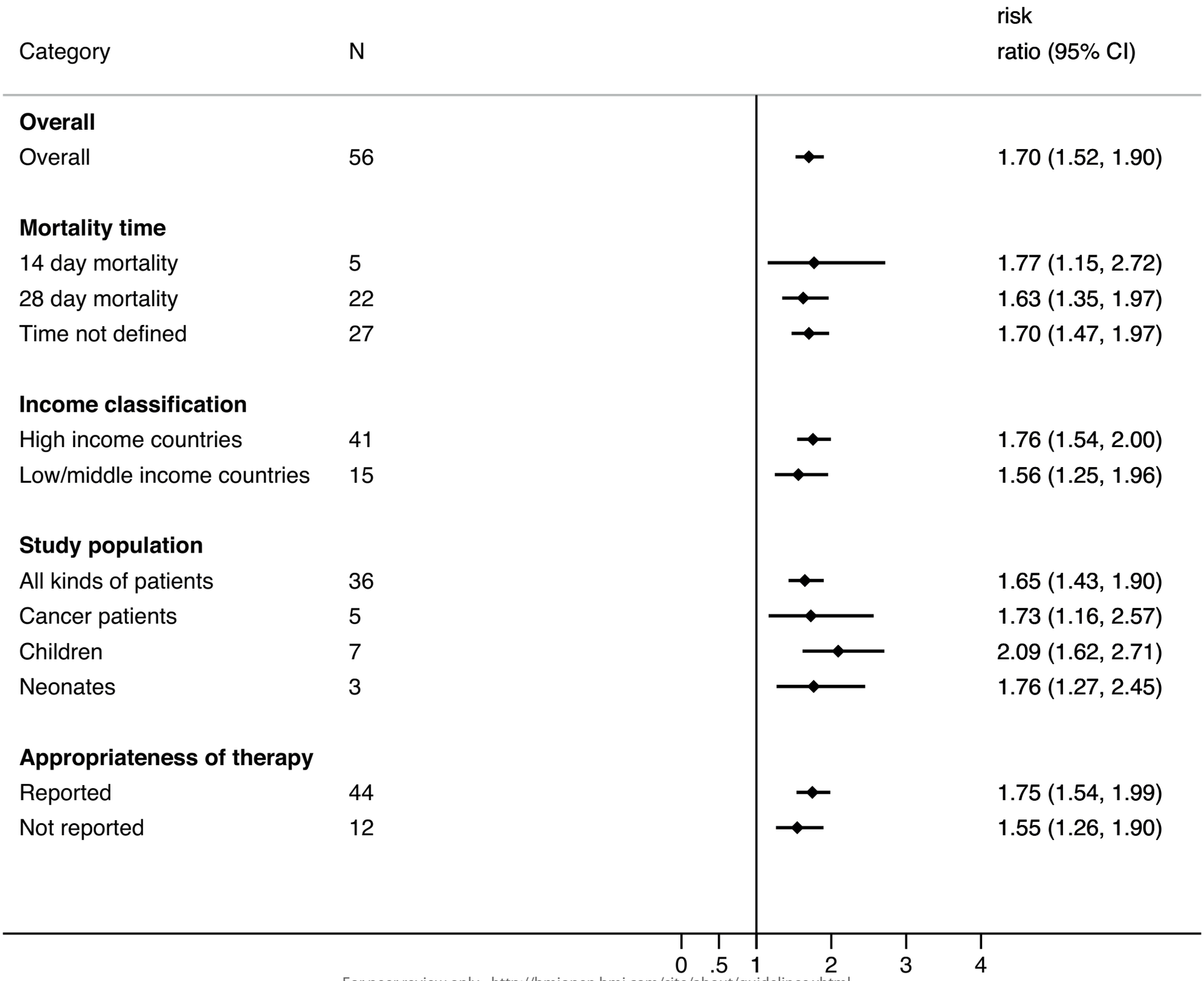
Figure 1: Literature search and study inclusion and exclusion

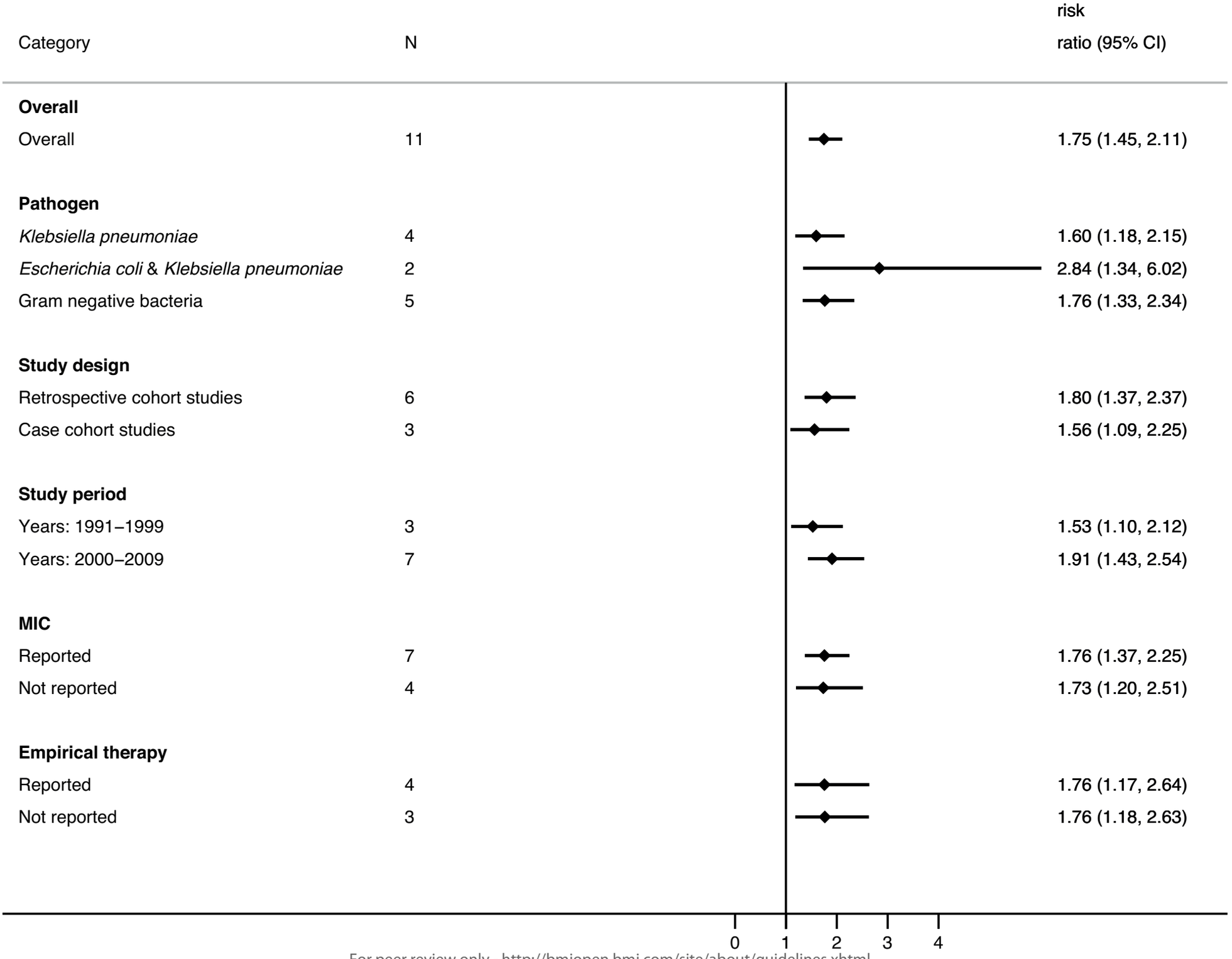
Figure 2: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections— subgroups not included in attributable mortality

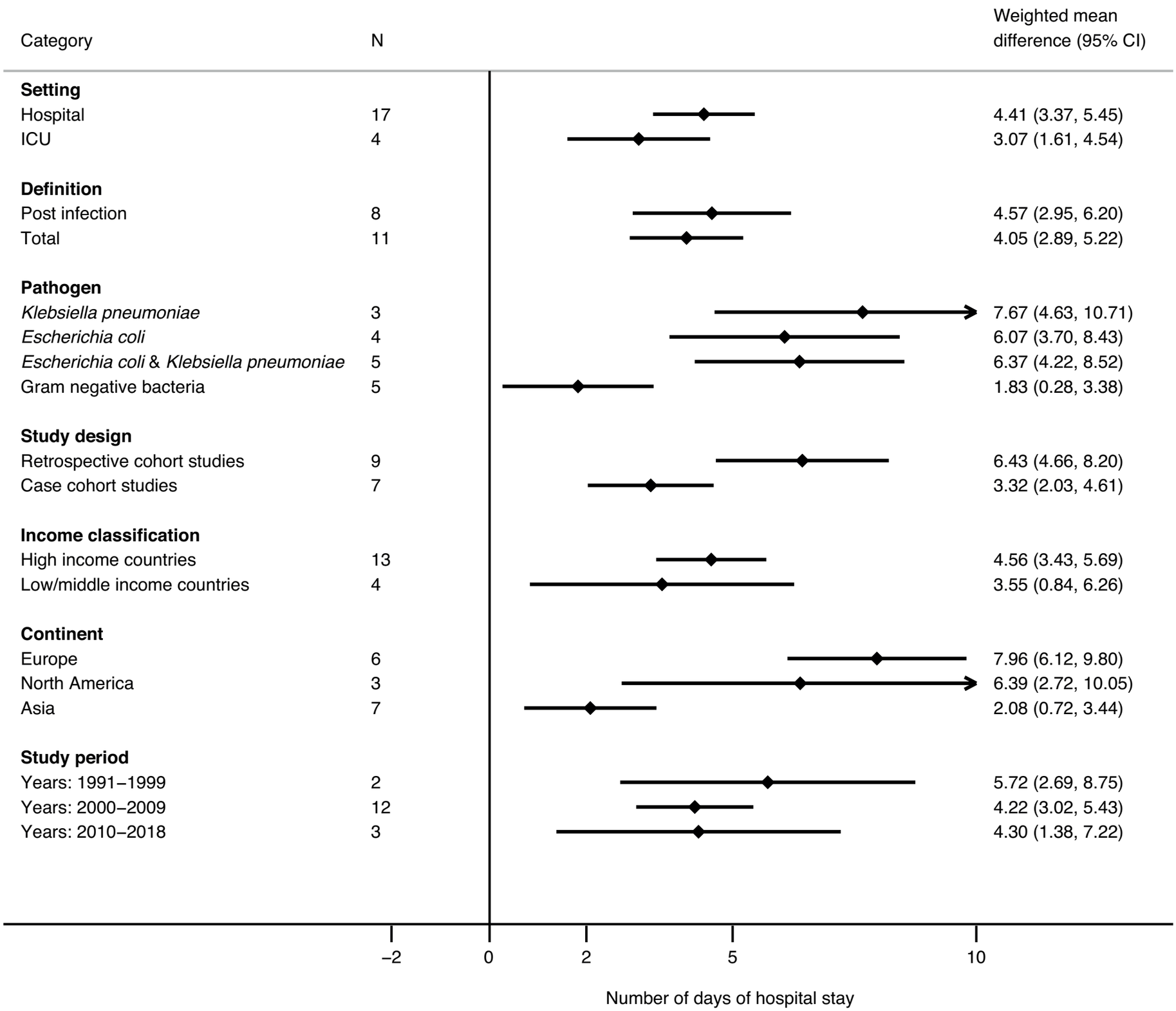
Figure 3: Pooled risk ratios for attributable mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

Figure 4: Weighted mean difference in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections


1006 articles identified through literature search
1006 abstracts screened
914 articles excluded
377 not studying impact of ESBL
392 no outcomes provided
105 no comparison / comparison not relevant
40 reviews
92 full-text articles assessed for eligibility
5 articles excluded
3 comparison not relevant
2 no outcomes provided
87 studies included in qualitative synthesis
3 articles excluded
3 insufficient data
84 studies included in quantitative synthesis (meta-analysis)




Category
N
risk ratio (95% CI)
Overall
Overall 11 1.75 (1.45, 2.11)
Pathogen
Klebsiella pneumoniae 4 1.60 (1.18, 2.15)
Escherichia coli & Klebsiella pneumoniae 2 2.84 (1.34, 6.02)
Gram negative bacteria 5 1.76 (1.33, 2.34)
Study design
Retrospective cohort studies 6 1.80 (1.37, 2.37)
Case cohort studies 3 1.56 (1.09, 2.25)
Study period
Years: 1991–1999 3 1.53 (1.10, 2.12)
Years: 2000–2009 7 1.91 (1.43, 2.54)
MIC
Reported 7 1.76 (1.37, 2.25)
Not reported 4 1.73 (1.20, 2.51)
Empirical therapy
Reported 4 1.76 (1.17, 2.64)
Not reported 3 1.76 (1.18, 2.63)
0
1
2
3
4


Category
N
Weighted mean difference (95% CI)
Setting
Hospital 17 4.41 (3.37, 5.45)
ICU 4 3.07 (1.61, 4.54)
Definition
Post infection 8 4.57 (2.95, 6.20)
Total 11 4.05 (2.89, 5.22)
Pathogen
Klebsiella pneumoniae 3 7.67 (4.63, 10.71)
Escherichia coli 4 6.07 (3.70, 8.43)
Escherichia coli & Klebsiella pneumoniae 5 6.37 (4.22, 8.52)
Gram negative bacteria 5 1.83 (0.28, 3.38)
Study design
Retrospective cohort studies 9 6.43 (4.66, 8.20)
Case cohort studies 7 3.32 (2.03, 4.61)
Income classification
High income countries 13 4.56 (3.43, 5.69)
Low/middle income countries 4 3.55 (0.84, 6.26)
Continent
Europe 6 7.96 (6.12, 9.80)
North America 3 6.39 (2.72, 10.05)
Asia 7 2.08 (0.72, 3.44)
Study period
Years: 1991–1999 2 5.72 (2.69, 8.75)
Years: 2000–2009 12 4.22 (3.02, 5.43)
Years: 2010–2018 3 4.30 (1.38, 7.22)
−2
0
2
5
10
Number of days of hospital stay

Supplementary table S1: Study characteristics overview

Subgroup	All Studies	Bloodstream infections	Noninvasive infections
	87	**57**	**10**
Country			
South Korea [11,12,14,15,29,33,36,40,42,44,49,50,55,57]	14	9	2
Thailand [22,24,43,51-53,86]	7	3	
USA [8,16,26,30,46,59,67]	7	2	1
Spain [34,38,56,60,68,89,92]	7	4	2
Taiwan [10,37,62,69,80,82,94]	7	5	2
China [58,71,72,75,85]	5	4	
Israel [21,45,90,91]	4	3	
Germany [9,39,41,61]	4	3	
Italy [23,31,35]	3	3	
Japan [74,79,84]	3	3	
Tanzania [17,64,73]	3	3	
India [47,48,78]	3	1	1
Canada [63,65,83]	3	2	
UK [20,28,87]	3	3	
France [66,77]	2	1	1
South Africa [13,81]	2	1	
Brazil [13,81]	2	2	
Greece [88]	1	1	
Hungary [93]	1	1	
Lebanon [25]	1	-	
Malaysia [27]	1	-	1
Mexico [70]	1	1	
Saudi Arabia [18]	1	1	
Turkey [76]	1	1	
Continent			
Asia [10-12,14,15,18,21,22,23,25,27,29,33,36,37,40,42-45,47-53,55,57,58,62,69,71,72,74,74,78-80,82,84-86,90,91,94]	46	29	6
Europe [9,20,23,28,31,34,35,38,39,41,56,60,61,66,68,76,77,87-89,92,93]	22	17	3
North America [8,16,26,30,46,59,63,65,67,83]	10	4	1
Africa [13,17,64,73,81]	5	4	-
South America [19,32,70]	3	3	-
More than 1 continent [54]	1	-	-

Income group			
High-income countries [8-12,14-16,18,20,21,23,26,28-31,34-42,44-46,49,50,55-57,59-63,65-69,74,77,79,80,82-84,87-94,]	60	41	8
Low- and middle-income countries [13,17,19,22,24,25,27,32,43,48,51-53,58,64,70-73,75,76,78,81,85,86]	26	16	2
High-income countries AND Low- and middle-income countries [54]	1	-	-
Study design			
Case cohort study [8,10,22-26,29,38,42,44,53,56,59,61-63,65-67,83-85]	24	14	
Retrospective cohort study [9,11-15,18,19,21,27,31-36,39-41,43,45,46,48-52,57,58,69,71,72,74-76,79-82,86,87,91,93,94]	44	32	
Prospective cohort study [16,17,28,30,37,47,54,60,64,68,70,73,77,78,88-90,92]	18	11	
Year group			
1991-1999 [8,58,13,14,15,60,19,23,26,34,44,91,92]	13	10	-
2000-2009 [9-12,16-18,20-22,24,25,27-33,35-43,45,47-50,52,53,55,56,59,61,62,65-67,87-90,93,94]	49	31	6
2010-2018 [46,51,52,57,63,64,68-86]	25	16	4
Pathogen			
Escherichia coli [9,22,28,31,33-35,38,41,43,50,53,56,57,66,68,69,71,74,84,85,89,92]	23	16	3
Klebsiella pneumoniae [13,14,18,19,23,27,30,32,39,41,45,59,60,72,76,81,93,94]	17	11	1
E. coli and *K. pneumoniae* [8,11,12,15,24,26,36,41,42,44,46,48,49,52,55,58,61,67,83,86,87]	20	13	2
Gram-negative bacteria [10,16,17,20,21,25,29,37,40,47,51,54,62-65,70,73,75,77-80,82,88,90,91]	27	17	4
Study setting			
Entire hospital [8,9,14,16,18-25,27,28,31-36,38-44,46-48,50-53,56-58,60,63-67,71,72,74,80,83,84,88-94]	57	40	7
Intensive care unit [30,59,62,73,77-79,86,87]	9	5	1
Pediatric ward [15,17,26,49,55,76,81,86]	8	7	-
Neonatal ward [13,59,62,69,73]	5	3	-
Neonatal intensive care unit [59,62,73]	3	2	-
Medical ward [11,37,68]	3	-	2
Not provided [29,45]	2	-	-
Emergency Department [10,82]	2	2	-
Surgical ward [30,54]	2	-	-
Burn unit [30]	1	-	-
Oncology [70]	1	1	-
Referral centre for hepatopacreaticobiliary diseases [75]	1	-	-
Hematological [12]	1	1	-

Study population			
All kinds of patients [8-11,12,16,18-25,27,28,32,33,37-39,41-44,46-48,50-54,56,58,60,61,63-67,74,80,82-84,88,90-93]	55	36	7
Intensive care unit patients [30,77-79,85,87]	6	3	1
Children [15,17,26,49,55,76,81,86]	8	7	-
Neonates [13,59,62,69,73]	5	3	-
Cancer patients [31,49,57,70,89]	5	5	-
Immunocompromised patients [49]	1	1	-
Diabetic patients [94]	1	1	-
Elderly patients [68]	1	-	1
Patients with chemotherapy/stem cell transplantation [12,89]	2	2	-
Patients after prostatitis biopsy [40]	1	-	1
Lungs transplantation patients [45]	1	-	-
Hematological patients [71]	1	1	-
All except cardiothoracic therapy, transplant surgery, burns [72]	1	1	
Patients with pyogenic liver abscess [75]	1	-	-
Data reported			
Treatment information [8,10-11,21-24,28-36,38,42-47,49,50,52-63,65,66,68-94]	74	50	6
Appropriateness of treatment [8,10-12,14,15,17-19,21-24,28-36,38,42-44,46,47,49,50,52-54,56-58,60-63,65,66,68,70-72,74,75,77,79,81-84,87-94]	62	45	5
Empirical therapy [12,14,15,22,23,31,33-36,38,42,49,50,54,56,57,61,74,79,81,92]	22	16	2
Treatment outcome [8,10-19,23,24,28-36,38,42-47,49,50,52-55,57-63,65,66,70-72,74,76-79,81-84,86-90,92-94]	64	45	3
Minimum inhibitory concentration results [8,9,11,12,14-17,20-23,25,26,30,31,33-39,41,42,45,48-50,52-57,60,61,64,66,67,74-76,78,79,81,83-85,87,92,93]	52	34	4
AmpC genotyping [8,9,15,30,39,44,48,54,55,63,64,68,84]	13	6	2

Supplementary table S2: Characteristics for each study

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Lautenbach E[8]	1997-1998	USA	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality; LOS	Risk factors for infection with ESBL-producing pathogens, difference in clinical outcomes of infections: resistant vs. susceptible organisms	EC, KP
Kim SH[12]	2007-2008	South Korea	Cohort study, Retrospective	Non-ESBL-infection	Patients who received either chemotherapy or stem cell transplantation; neutropenic fever	Hematological ward, Others	All-cause mortality (28 day)	Risk factors for acquisition of ESBL, appropriateness of empirical antimicrobial therapy, clinical outcomes in relation to ESBL production	EC, KP
Chayakulkeere M[51]	2015-2015	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Prevalence & risk factors for infections with & antibiotic susceptibility patterns of & outcomes of patients infected with ESBL-producing-GNB	GNB
Apisarnthanarak A[52]	2003-2007	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Predictors for mortality associated with community-onset BSI with ESBL-producing pathogens, initial empirical antimicrobial regimens, associated hospital resource utilisation,costs accrued after diagnosis of BSI	EC, KP
Apisarnthanarak A[53]	2003-2004	Thailand	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Mortality associated with community-onset infection due to ESBL-producing pathogens, associated hospital resource use, post-infection hospital cost	EC
Jean SS[54]	2010-2011	Portugal, Columbia, the Philippines, Taiwan, Thailand	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Surgical ward	Attributable mortality, LOS	Clinical impact on hospitalised patients with community-acquired complicated intra-abdominal infection: ESBL-producing- vs. non-ESBL-producing pathogens	GNB
Lee J[55]	1999-2005	South Korea	interventional studies	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	impact of a change in antibiotic policy on ESBL-prevalence	EC, KP
Briongos-Figuero L.S[56]	2009-2010	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Characteristics &associated risk factors for EBSL-enterobacteria-UTIs	EC
Ha YE[57]	2010-2012	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with cancer	Entire hospital	All-cause mortality (28 day)	Clinical &molecular epidemiology of ESBL-EC bacteraemia, clinical impact of ESBLs on patient outcome	EC
Du B[58]	1997-1999	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for nosocomial ESBL-EC- and ESBL-KP- bacteraemia & influence on patient outcome.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Stone PW[59]	2001	USA	Case cohort study	Non-ESBL-infection	Neonates at NICU	NICU	LOS	costs of interventions aimed at controlling the outbreak, attributable length of stay associated with infection and colonisation with ESBL-KP	KP
Pillay T[13]	1995-1996	South Africa	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Use of piperacillin/tazobactam in treatment of KP- infection	KP
Kim BN[14]	1999-2000	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, LOS	Prevalence & clinical characteristics of ESBL-KP- bacteraemia, impact of ESBL- production on outcome of patients with KP-bacteraemia in endemic situation.	KP
Kim YK[15]	1993-1998	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Risk factors & clinical outcomes & clinical responses to treatment of ESBL-EC- and ESBL-KP-bacteraemia, prevalence and types of their ESBLs	EC, KP
Bhavnani SM[16]	2001-2002	USA	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Risk factors for occurrence of invasive ESBL-EC- and ESBL-KP-infections, factors associated with clinical outcome, drug regimens for treatment of infections associated ESBL/non-ESBL strains in real-life clinical practice, clinical response rates for patients treated with cephalosporins/other classes of antimicrobial agents, /carbapenems, clinical response for those patients with infection associated with ESBL and non–ESBL-producing strains with MIC values V8 Ag/mL treated with cephalosporins.	GNB
Blomberg B[17]	2001-2002	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates, children	Pediatric ward	All-cause mortality	Prevalence & clinical implications of ESBL production in EC-,KP-, Salmonellae- septicemia	GNB
Pena C[60]	1993-1995	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Clinical epidemiology& outcome of ESBL-KP- bacteraemia, relevance of ESBL strains in mortality of patients with hospital-acquired KP-BSI.	KP
Kola A[61]	2002-2004	Germany	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Outcomes of ESBL-EC- and ESBL-KP-infections	EC, KP
Tsai MH[62]	2001-2012	Taiwan	Case cohort study	Control group: non-ESBL-infection, second control group: all hospitalised patients	Neonates at NICU	NICU	Attributable mortality, all-cause mortality, LOS	Clinical features& risk factors& molecular epidemiology of ESBL-GNB	GNB
Maslikowska JA[63]	2010-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	Differences in clinical & microbiological outcome, mortality, and/or hospital resource use: ESBL-EC- and ESBL-Ks- vs non-ESBL-EC- and non-ESBL-Ks-infections	GNB

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Onken A[64]	2012-2013	Tanzania	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Most common bacterial pathogens causing BSI, antimicrobial susceptibility	GNB
Nguyen ML[65]	2005-2010	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Risk factors for & patient outcomes associated with ESBL-EC- and ESBL-Ks- bacteraemia, appropriateness of empiric antibiotic therapy & effect of inappropriate empiric therapy on outcomes	GNB
Denis B[66]	2005-2009	France	Case-control study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Prevalence & risk factors for ESBL-EC bacteraemia, impact on length of stay &30day mortality	EC
Chopra T[67]	2004-2009	USA	Case cohort study	Case 2(Control1): non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Predictors of ESBL-EC- and ESBL-KP-BSI, focus on cefepime exposure.	EC, KP
Panhotra BR[18]	2001-2003	Kingdom of Saudi Arabia	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors & clinical outcome of ESBL-KP-bacteraemia (hospital acquired)	KP
Marra AR[19]	1996-2001	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	ESBL-KP- associated mortality	KP
Skippen I[20]	2003-2005	UK	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-invasive transmission of organism in the healthcare setting	GNB
Schwaber MJ[21]	2000-2003	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Outcomes of ESBL-production in Enterobacteriaceae-bacteraemia.	GNB
Apisarnthanarak A[22]	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All adult patients	Entire hospital	All-cause mortality, LOS	Clinical & molecular epidemiologic factors associated with community onset ESBL-EC- infections, hospital resource utilisation, estimate costs associated with medical care (hospitalised patients)	EC
Tumbarello M[23]	1999-2003	Italy	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS, ICU-LOS	Factors associated with isolation of ESBL- KP-strains	KP
Zeistner R[9]	2008-2010	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital,	All-cause mortality, LOS	Difference in mortality: ESBL-EC-BSIs vs. non-ESBL-EC-BSIs, molecular epidemiology of ESBL-positive isolates	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Apisarnthanarak A[24]	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-infections (healthcare associated)	EC, KP
Kanafani ZA[25]	2003	Lebanon	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Epidemiology of infections with ESBL-EC and ESBL-Ks at AUBMC risk factors & outcomes of infections - focus on effect of prior antibiotic administration & the risks imparted by specific classes of antimicrobial agents	GNB
Zaoutis TE[26]	1999-2003	USA	Case cohort study	Non-ESBL-infection	Children	Entire hospital	All-cause mortality, LOS	Risk factors & outcomes associated with ESBL-EC-and ESBL-KP-BSI	EC, KP
Loh LC[27]	2003-2004	Malaysia	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Impact of ESBL-KP-respiratory tract infections on hospital mortality, requirement for mechanical ventilation & length stay	KP
Melzer M[28]	2003-2005	UK	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Differences in mortality & length of hospital stay &time from bacteraemia to death in patients with ESBL-EC- vs. non-ESBL-EC-bacteremic-infection	EC
Song KH[29]	2000-2006	South Korea	Case cohort study	Non-ESBL-infection	Patients with spontaneous bacterial peritonitis	Not provided	All-cause mortality (28 day)	Outcomes of ESBL-EC-and ESBL-Ks- vs non-ESBL-EC-and ESBL-Ks-SBP (based on isolation from ascites), impact of ineffective initial antimicrobial therapy on outcome in patients with ESBL-EC- and ESBL-Ks-SBP, risk factors for infection by ESBL-producing microorganisms.	GNB
Bennett JW[30]	2004-2008	USA	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU, Surgical ward, Burn unit	All-cause mortality (28 day)	ESBL types and strain variability, presence of host factors to determine potential role in morbidity and mortality during ESBL-KP-infections	KP
Trecarichi EM[31]	2000-2007	Italy	Cohort study, retrospective	Non-ESBL-infection	Patients with hematological malignancies	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality in patients suffering from hematological malignancies with concurrent EC-bacteraemia. Focus on impact of ESBL- production & fluoroquinolone resistance by bacterial isolates	EC
Tuon FF[32]	2006-2009	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Risk factors & mortality rate in ESBL-KP-bacteraemia	KP
Kang CI[33]	2008-2009	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors of ESBL-EC among community-onset bacteraemia, treatment outcomes	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Pena C[34]	1996-2003	Spain	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality among patients with EC- infections	EC
Tumbarello M[35]	2006	Italy	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	ICU, Medical ward, Entire hospital, surgical wide	All-cause mortality (21 day), LOS	Clinical &economic impacts of ESBL production, inadequate Initial Antibiotic Therapy of EC-BSI	EC
Kang CI[36]	2006-2009	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality (28 day)	Impact of ESBL-producing bacteraemia on outcome in patients with hematologic malignancy.	EC, KP
Wu YH[37]	2009-2012	Taiwan	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Medical ward	LOS	Host-related risk factors for community-onset UTI due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production, clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens	GNB
Rodriguez-Bano J[38]	2004-2006	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Epidemiology& risk factors (focus on previous antimicrobial use) & mortality rate for patients with ESBL-EC-COBSI	EC
Gürtnke S[39]	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Distribution of ESBL genotypes, hospital mortality in cases of ESBL-KP-BSI	KP
Oh MM[40]	2006-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients after Prostatitis Biopsy	Entire hospital	LOS	Impact of ESBL-positive-strains on clinical course & progression to chronic prostatitis in patients with postbiopsy acute prostatitis.	GNB
Leistner R[41]	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Financial disease burden attributable to ESBL-positive species in cases of EC-and KP-BSI	EC, KP
Lin JN[10]	2005-2009	Taiwan	Case cohort study	Non-ESBL-infection	All kinds of patients	Emergency Room	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Clinical & microbiological characteristics, risk factors for acquisition of infection, prescription of initial empirical antibiotics mortality rate of infection	GNB
Ku NS[42]	2006-2010	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Clinical usefulness of breakpoints for treatment of Enterobacteriaceae-bacteraemia, (focus on EC- and Ks-bacteraemia): CLSI 2009- vs. CLSI 2010-guidelines.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Anunnatsiri S[43]	2005-2006	Thailand	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Incidence of ESBL-EC-septicemia, factors associated with infection & clinical outcomes	EC
Kang CI[44]	1998-2002	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Hospital-wide	All-cause mortality (28 day)	Risk factors for mortality & treatment outcome of ESBL-EC- and ESBL-KP-BSI	EC, KP
Raviv Y[45]	2004-2007	Israel	Cohort study, retrospective	Control group: non-ESBL-infection, second control group: no infection	patients with lung transplantation	Not provided	All-cause mortality (28 day)	Outcomes of lung transplant recipients infected by CRKP and ESBL carbapenem-sensitive KP (referred to MDR-KP)	KP
Kim HJ[11]	2005-2010	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Medical ward	All-cause mortality (28 day), LOS	Clinical outcome of patients with biliary tract infection: ESBL-producing bacterial isolates vs. non-ESBL-producing-bacterial isolates, predictors of poor prognosis, impact of ineffective antimicrobial therapy on clinical outcome	EC, KP
MacVane SH[46]	2011-2012	USA	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	clinical & economic outcomes of patients with ESBL-EC- and ESBL-KP-UTI vs. non-ESBL-EC- and non-ESBL-KP-UTI	EC, KP
Abhilash KP[47]	2007	India	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Prevalence & risk factors & outcome of antibiotic treatment among hospitalised patients with ESBL-EC- and ESBL-Ks-BSI	GNB
Shanthi M[48]	2006	India	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Prevalence & impact on clinical outcome of ESBL-production among nosocomial isolates of EC & KP	EC, KP
Han SB [49]	2009-2013	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children (immunocompromised, with cancer, neutropenic fever)	Pediatric ward	Attributable mortality, all-cause mortality (28 day)	Clinical outcomes of ESBL-EC- and ESBL-KP-bacteraemia & their antibiotic susceptibilities	EC, KP
Lee S[50]	2009-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with Acute Pyelonephritis	Entire hospital	All-cause mortality (14 day), LOS	Impact of ESBL on clinical outcomes of Acute Pyelonephritis treated with empirical ceftriaxone (which was inappropriate for ESBL-producing organisms)	EC
Artero A[68]	2013-2015	Spain	Cohort study, prospective	Non-ESBL-infection	Elderly	Medical ward	All-cause mortality, LOS	Identify clinical factors to predict ESBL-EC among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-EC	EC

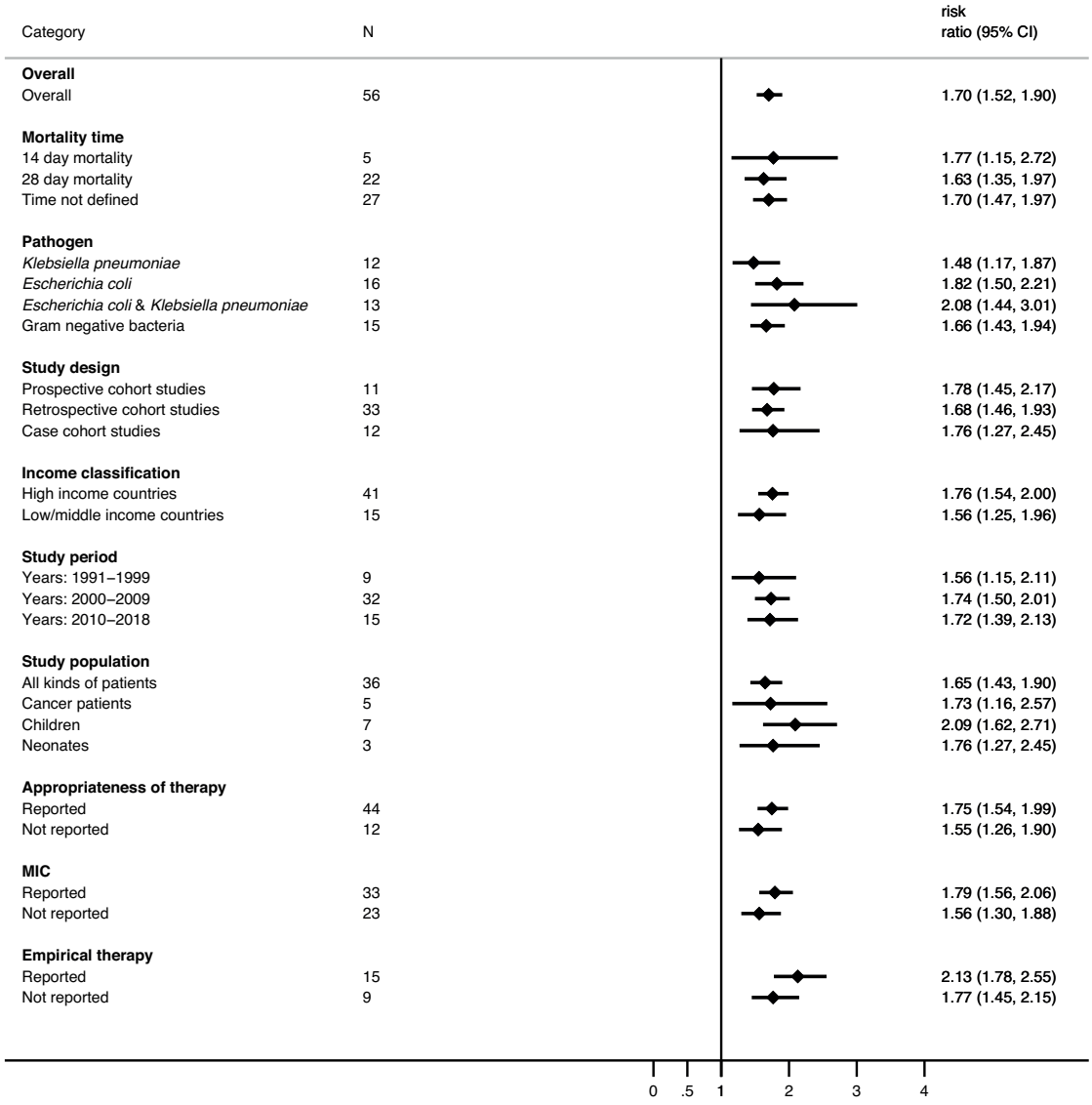
	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Chen IL [69]	2004-2015	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Compare the clinical characteristics & laboratory data of preterm babies with EC BSI: survival vs. nonsurvival groups, ESBL vs non-ESBL groups, determine the predictive factors of EC BSI in preterm babies	EC
Islas-Munoz B[70]	2016-2017	Mexico	Cohort study, prospective	Non-ESBL-infection	Cancer patients	Oncological ward	All-cause mortality (28 day)	Evaluate the clinical epidemiological characteristics & risk factors associated with mortality in cancer patients with BSI-special emphasis on MDR bacteria	GNB (and others)
Ma J[71]	2012-2015		Cohort study, retrospective	Non-ESBL-infection	Patients with hematological diseases	Entire hospital	All-cause mortality (28 day)	Evaluate the antimicrobial resistance & clinical features & risk factors for septic shock & death of nosocomial EC-BSI	EC
Man MY[72]	2009-2016	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients, except patients from Burn unit, transplant surgery ward or with thoracic therapy	Entire hospital	All-cause mortality (28 day)	Evaluate the incidence & clinical characteristics & outcomes of patients with KP BSI in critical care & general ward settings	KP
Marando R[73]	2016	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates	NICU	All-cause mortality	Investigate factors associated with ESBL-PE neonatal sepsis & mortality among neonates, characterise selected isolates to show virulence potential & transmission dynamics	GNB
Namikawa H[74]	2011-2015	Japan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate clinical characteristics of patients with ESBL-EC-BSI	EC
Shi SH[75]	2008-2015	China	Cohort study, retrospective	Non-ESBL-infection	Patients with pyogenic liver abscess	Centre for hepatopancreaticobiliary diseases	All-cause mortality, LOS	Aetiology & morbidity & clinical characteristics of pyogenic liver abscess caused by ESBL-PE	GN
Tanir Basaranoglu S[76]	2011-2015	Turkey	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	Assess risk factors for health care associated ESBL-KP-BSI in children, analyze clinical outcomes: ESBL-KP vs. non-ESBL-KP	KP
Razazi K[77]	2009-2015	France	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality, LOS, ICU-LOS	Determine, among ESBL-PE carriers, the prevalence & associated factors & clinical impact of ESBL-PE pneumonia, determine factors associated with ICUAP caused by carbapenem-resistant bacteria	GNB

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Ray S[78]	2014-2016	India	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Investigate spectrum of microbial resistance pattern in the community and their effects on mortality	GNB
Haruki Y[79]	2006-2016	Japan	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Compare the clinical characteristics & outcomes of critically ill patients in an ICU, who were hospitalised for BSI caused by ESBL-EC or non-ESBL-EC.	GNB
Lin WT[80]	2009-2014	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate the clinical manifestations & bacteriological features of culture-proven, GNB arthritis	GNB
Guys H[81]	2006-2011	South Africa	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Describe the clinical presentation of KPBSI, risk factors associated with ESBL-KPBSI, antibiotic susceptibility patterns of the KP isolates & KPBSI mortality including factors associated with in-patient mortality	KP
Lee CC[82]	2008-2013	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Emergency Department	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Analyse the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics & bacteraemia severity by using a propensity-matched analysis (PSM)	GNB
Huang YY[83]	2011-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Determine cumulative incidence of ESBL urosepsis, identify major risk factors for ESBL urosepsis, determine impact of international travel on development of ESBL urosepsis	EC, KP
Komatsu Y[84]	2008-2013	Japan	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Identify risk factors & clinical outcomes in patients with BSI due to ESBL- or carbapenemase-producing EC, determine prevalence & genetic background	EC
Liu MM [85]	2011-2016	China	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	ICU-patients	ICU	All-cause mortality	Identify risk factors for ESBL-producing ECBSI among carriers at ICU	EC
Nivesvivat T[86]	2010-2017	Thailand	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality, LOS	Determine prevalence, risk factors & clinical outcomes of ESBL-producing EB in paediatric BSI	EC, KP

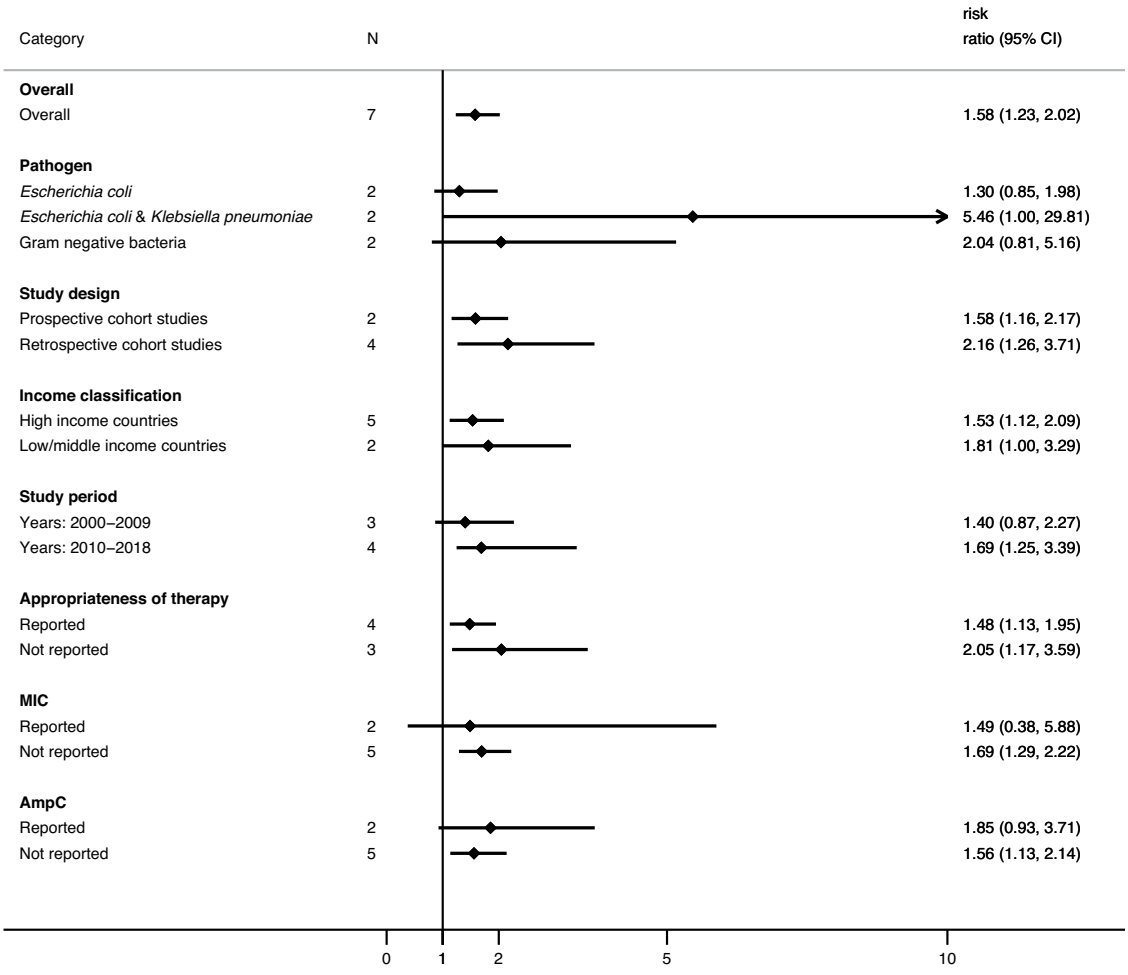
	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Cordery RJ[87]	2004-2006	UK	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Elucidate specific risk factors for the acquisition of ESBL infection in the ICU; all-cause mortality (in ICU) compared in patients with infections due to ESBL- and non-ESBL-producing organisms	GNB
Paikos GL[88]	2003-2005	Greece	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Identify risk factors associated BSI caused by integron-carrying EB; evaluate the consequences of these genetic elements on patient outcome	GNB
Gudiol C[89]	2006-2008	Spain	Cohort study, prospective	Non-ESBL-infection	Cancer patients and hematopoietic stem cell transplant patients	Entire hospital	All-cause mortality	Assess clinical features, risk factors, molecular epidemiology & outcome of ESBLEC BSI in hospitalised cancer patients	EC
Marchaim D[90]	2006-2008	Israel	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Define predictors & outcomes of ESBL BSI among patients with bacteraemia due to EB upon hospital admission	GNB
Menashe G[91]	1997	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Determine: prevalence of ESBL-P organisms among adult patients with nosocomial EB BSI treated in our institution; association between ESBL production & resistance to other antibiotics; clinical characteristics of patients with nosocomial ESBL-P BSI compared with those infected with non-producing strains; impact of ESBL production on outcome of patients with nosocomial EB BSI	GNB
Ortega M[92]	1991-2007	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Describe source, resistance rate to fluoroquinolone & beta-lactam antibiotics and mortality of EC BSI episodes in a single institution; identify predictive factors for isolation of fluoroquinolone-resistant or ESBL- producing strains.	EC
Sziglyi M[93]	2005-2008	Hungary	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality,	Investigate risk factors for & outcomes of BSI caused by ESBL-producing and ESBL-non-producing KP	KP
Tsai SS[94]	2005-2006	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Diabetic patients	Entire hospital	All-cause mortality	Analyze characteristics, risk factors & outcomes of diabetic patients with community- vs. hospital-acquired KP BSI	KP

EC = *Escherichia coli*
KP = *Klebsiella pneumoniae*
GNB = Gram-negative bacteria
BSI = Bloodstream infection
UTI = Urinary tract infection
ICU = Intensive care unit
NICU = Neonatal intensive care unit
ESBL-PE = Extended-spectrum beta-lactamase-producing Enterobacteriaceae
EB = Enterobacteriaceae
LOS = Length of stay

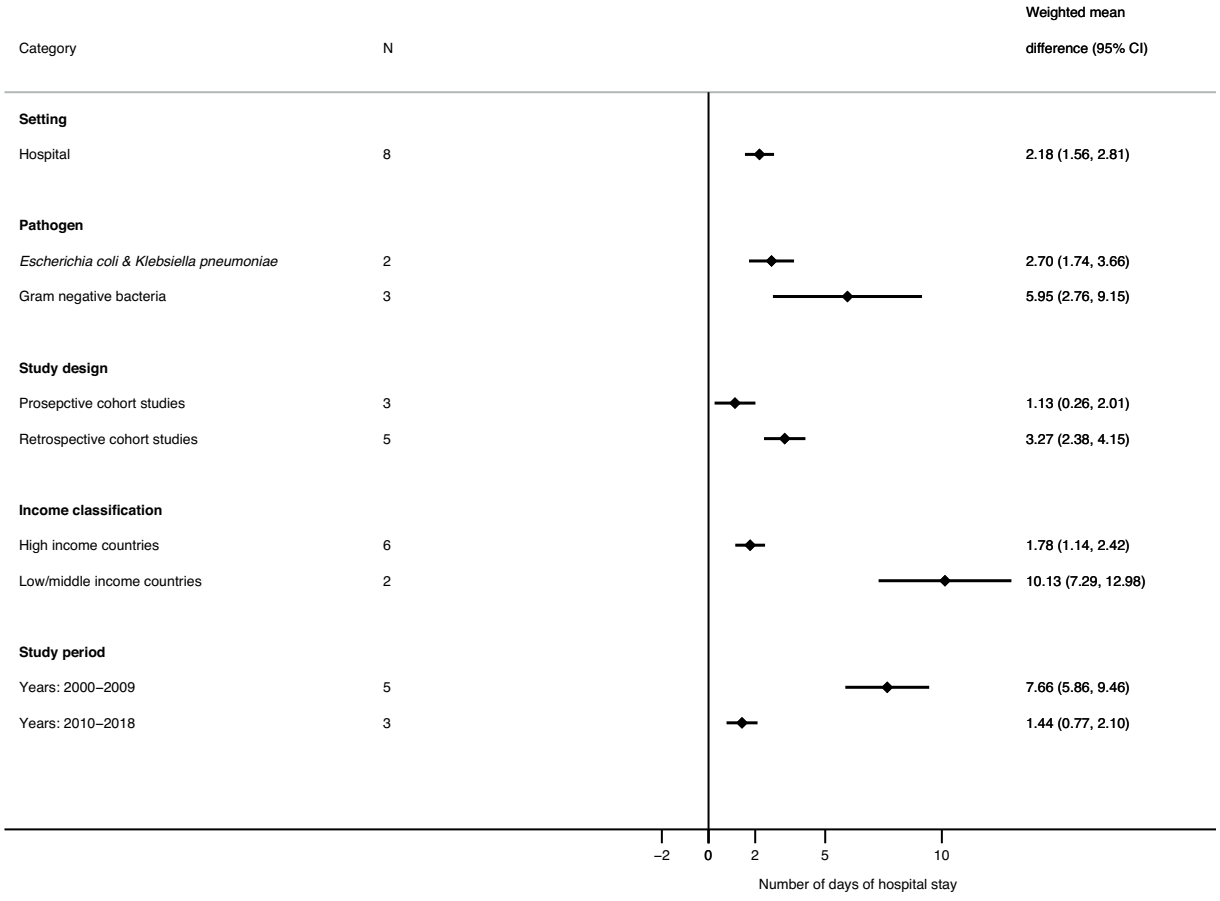
Supplementary figure S1: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections—all subgroups



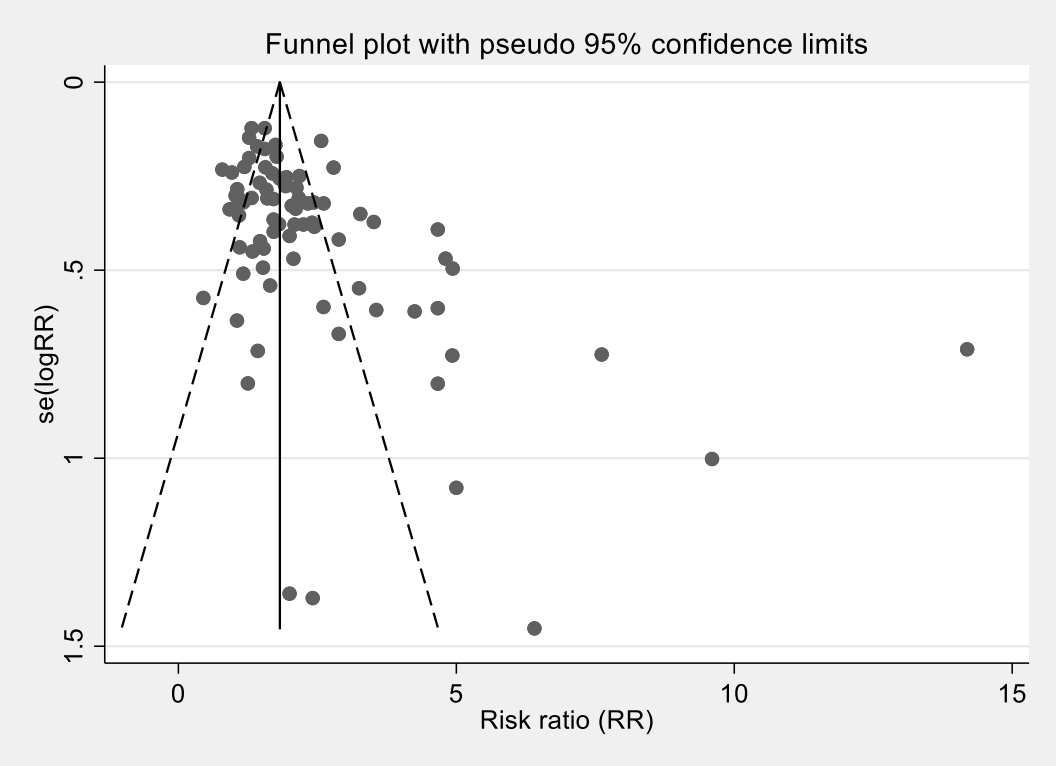
Supplementary figure S2: Pooled risk ratios for all-cause mortality in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary figure S3: Weighted mean differences in length of hospital stay in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections

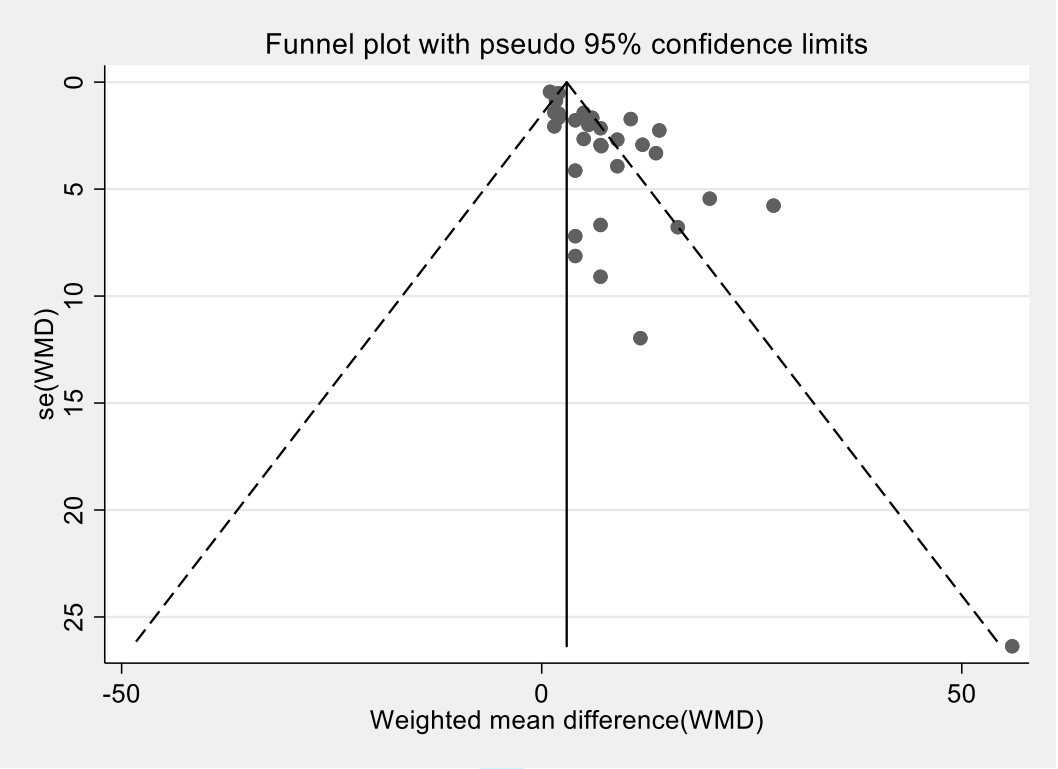


Supplementary figure S4: Funnel plot of risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



The y axis se(logRR) is the standard error of the log risk ratio Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure S5: Funnel plot of weighted mean differences in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



The y axis se(WMD) is the standard error of the weighted mean difference. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	suppl.material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	21-23 and suppl.material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

BMJ Open

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030266.R1
Article Type:	Original research
Date Submitted by the Author:	19-Sep-2019
Complete List of Authors:	Shamsrizi, Parichehr; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Gladstone, Beryl Primrose ; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Carrara, Elena; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Luise, Dora; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Cona, Andrea; ASST Santi Paolo e Carlo, Clinic of Infectious and Tropical Diseases, Department of Health Sciences Bovo, Chiara; Integrated University Hospital of Verona, Medical Direction Tacconelli, Evelina; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Epidemiology
Keywords:	Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

AUTHORS:

Parichehr Shamsrizi[1], Beryl Primrose Gladstone[1], Elena Carrara[2], Dora Luise[2], Andrea Cona[3], Chiara Bovo[4], Evelina Tacconelli[1,2]

AFFILIATIONS:

1) Division of Infectious Disease, Department of Internal Medicine I, DZIF Partner site, Tübingen University Hospital, Tübingen, Germany
2) Division of Infectious Disease, Department of Diagnostic and Public Health, University Hospital of Verona, Verona, Italy
3) Clinic of Infectious and Tropical Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
4) Medical Direction, University Hospital of Verona, Verona, Italy

CORRESPONDING AUTHOR: Elena Carrara, MD

Address: Division of Infectious Disease, Department of Diagnostic and Public Health, University Hospital of Verona, Verona, Italy

Piazzale L.A. Scuro 10, Dipartimento di Malattie Infettive, Policlinico Borgo Roma, 37100 Verona, Italy.

Phone number: +39 3339566252

Email: elena.carrara@univr.it

WORD COUNT: 2701

ABSTRACT

Objective To assess the variation of effect estimates in the analysis of mortality and length of stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*.

Design Systematic review and meta-analysis

Methods Literature search for clinical studies from 1 January 1960 to 1 October 2018 was conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream infections (BSIs) and non-invasive infections. Any change in the effect estimates was assessed by grouping studies according to design, setting, economy-based country classification, reporting period, microbiological aetiology, infection type, and adjustment for appropriateness of empirical treatment. The impact of ESBL production was calculated using random effect meta-analysis and heterogeneity was evaluated by I^2 statistics and metaregression.

Results Eighty-four studies including 22,030 patients and 149 outcome measures were included in the meta-analysis. Most studies were retrospective cohorts from high-income countries, providing unadjusted estimates. ESBL production in patients with BSIs (56 studies) increased the RR for all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; p<0.001), attributable mortality (16 studies) by 1.75 (95% CI: 1.448-2.108; p<0.001), and WMD in the intensive care unit by 3.07 days (95% CI: 1.61-4.54; p<0.001). WMD in hospital LOS was significantly higher in BSIs (4.41 days; 95% CI: 3.37-5.46; p<0.001) and non-invasive infections (2.19 days; 95% CI: 1.56-2.81; p<0.001). Subgroup analyses showed variation of estimates by study design, population, strain, and assessment of appropriateness of empiric treatment. High heterogeneity was observed in all analyses.

Conclusions Current evidence of the clinical burden of infections caused by ESBL-producing bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from retrospective studies. Despite these limitations, ESBL production in strains causing BSIs seems associated with higher all-cause and attributable mortality and longer hospitalisation.

KEYWORDS

Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Evidence of the impact of ESBL production on mortality and length of stay in strains causing invasive and non-invasive infections was collected systematically.
- Effect of multiple epidemiological and clinical variables was assessed in the calculation of estimates.
- Heterogeneity among studies was assessed.
- Only few studies had been performed in high-risk populations or low-income countries.

INTRODUCTION

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* are responsible for high morbidity and mortality worldwide.[1,2,3] The 2018 World Health Organization list of antibiotic-resistant pathogens identified mortality as the most important criteria to prioritise bacteria for research and development of new, effective antibiotics.[1] In this prioritisation exercise, ESBL-producing *Enterobacteriaceae* were designated a critical priority because of their high all-cause mortality and high prevalence globally in healthcare-associated and community-acquired infections. The incidence and attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing *Enterobacteriaceae*, in European countries has been recently estimated using a modelling analysis.[4] In 2015 ESBL-producing *Escherichia coli* was responsible for almost 300,000 infections in Europe and 9,000 attributable deaths, and ESBL-producing *Klebsiella pneumoniae* caused around 70,000 infections and more than 3,500 deaths. The major limitation of this analysis is the sparseness of evidence on mortality due to ESBL-producing bacteria, which was limited largely to studies conducted in high-income countries.

Two systematic reviews have been performed to define the impact of ESBL production on mortality due to *Enterobacteriaceae*.[2,3] Both meta-analyses included studies targeting bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated bacteraemia compared to non-ESBL *Enterobacteriaceae* bacteraemia. A major drawback of the analyses, highlighted by the authors, was the lack of control for confounding and limited adjustment for empiric therapy. No systematic review has been performed to assess attributable mortality and other indicators of clinical impact such as length of stay (LOS).

Because estimates of clinical burden drive policy design for antibiotic stewardship and infection control interventions, precise and current estimates are essential. The objective of this systematic review and meta-analysis was to assess the variation of effect estimates in the analysis of mortality and LOS in patients with infections due to ESBL-producing *Enterobacteriaceae*.

METHODS

Literature search strategy

The search was performed by 2 researchers (BPG and PS) in PubMed on 05 October 2018 using search terms (supplementary table S1) relevant to the following combinations: (ESBL AND Escherichia coli AND mortality) OR (ESBL AND Klebsiella pneumoniae AND mortality) OR (ESBL AND Escherichia coli AND length of stay OR length of hospitalisation) OR (ESBL

AND Klebsiella pneumoniae AND length of stay OR length of hospitalisation). Reference lists of retrieved articles were also searched.

Eligibility criteria

We included all clinical studies with a comparison group assessing all-cause mortality, attributable mortality, and overall LOS and intensive care unit stay (ICU) LOS in hospitalised patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018 irrespective of the clinical setting and study design were included. No language restriction has been applied. Diagnostic studies, reviews, case reports, non-clinical studies, and abstracts of conference presentations were not included.

Data extraction

Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted data. In case of disagreement, a third reviewer (DL) was consulted. Extracted data were collected in an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of publication, year of study, time of data collection, study design, comparison group, study setting, population, aetiology, type and site of infection, and raw data related to mortality and LOS/ICU-LOS. Countries were classified as high-, middle-, or low-income using the World Bank Atlas method.[5] Adjusted effect estimates such as odds ratios (ORs) or hazard ratios and quality indicators such as reporting of antibiotic therapy, appropriateness of empirical treatment, resistance mechanisms, and minimum inhibitory concentrations (MICs) were also extracted.

Mortality data were extracted as all-cause mortality or attributable mortality as defined in the studies. Where available, prespecified time periods for mortality assessment (i.e., 14 days, 28 days, in-hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean and standard deviation or median and interquartile range.

Data analysis

The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in patients with ESBL infections compared with those in patients with non-ESBL infections and, where available, with uninfected patients. The impact of ESBL production on attributable and all-cause mortality was calculated with random effect meta-analysis and expressed as RR with 95% confidence interval (CI). WMD in days with 95% CI was calculated to express the excess in LOS and ICU-LOS.

Variation of the effect estimate was assessed by grouping the studies according to the following study/outcome characteristics: mortality time assessment (7 vs 14 days), aetiology (*E. coli* vs *K. pneumoniae*), clinical setting (paediatric, oncology, ICU), economic country areas (high-income countries [HICs] vs low- and medium-income countries [LMICs]), study design, assessment of empiric therapy, and year. The source of infection was assessed and analysis of mortality focused on BSIs while LOS was determined for BSIs and non-invasive infections (i.e., urinary tract infections, respiratory tract infections, surgical site infection) due to limited reporting.

Subgroup analysis was computed only if more than 2 studies were available for each group. Heterogeneity was evaluated by using I^2 statistics and metaregression. Overall significance testing was carried out using Wald tests adjusted using the Bonferroni correction. The unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment. Reporting and publication bias was presented in funnel plots (supplementary figure 1 and 2) and tested by Egger's test. Statistical analyses were performed using Stata version 15. Risk of bias was assessed independently by two authors (PS, DL) using the Newcastle - Ottawa quality assessment scale for cohort studies.[6] Studies were classified as low, moderate, or high quality according to AHRQ standards (supplementary table S2). All meta-analyses were performed in accordance with the Cochrane Collaboration recommendations[7] and reported according to the PRISMA statement.[8]

The protocol is available online.

(https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf)

Patient and Public Involvement

There was no patient or public involvement in this systematic review of published literature.

RESULTS

Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an evidence base of 87 studies (Figure 1).[9-95] The 87 studies included in the qualitative analysis were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies), Thailand (7), USA (7), Taiwan (7), and Spain (7). Sixty (68.9%) studies were performed in HICs, 26 (29.9%) in LMICs, and 1 included both HICs and LMICs.[55] About half (44, 50.6%) were retrospective cohort studies, 24 (27.6%) case cohort studies, and 18 (20.7%) prospective

cohort studies; 1 study had an interventional design.[56] The comparison group was patients with infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-infected patients in 2 (2.3%), and both control groups in 3 (3.5%). Most (57, 65.5%) studies included data from the entire hospital, while a few focused on specific settings, mainly ICUs (9, 10.3%) and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were *E. coli* (23, 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is provided in online supplementary table S3.

Because data in 3 studies [21,60,86] were insufficient for quantitative analysis, 84 (96.6%) studies were included in the meta-analysis analysing data from 22,030 patients and 149 outcome measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study characteristics for all studies are provided in online supplementary table S4. 49 (58.3%) studies were of high quality, 23 (27.3%) were of moderate quality, and 12 (14.3%) were of low quality (supplementary table S5).

All-cause mortality

All-cause mortality was reported in 81 studies including 21,942 patients (56 on BSIs and 7 on non-invasive infections). ESBL production in patients with BSIs increased all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; p<0.001; I^2=45.3%; p<0.001). The RR increased over time from 1.56 (95% CI: 1.15-2.11; p=0.004) in 1991-1999 to 1.74 (95% CI: 1.50-2.01; p<0.001) in 2000-2009, and it was stable in 2010-2018 (1.72, 95% CI: 1.39-2.13; p<0.001). The RR was higher in studies assessing appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; p<0.001) than in those that did not (RR=1.55; 95% CI 1.26-1.90; p<0.001). The subgroup analysis by pathogen showed that ESBL production increased the RR in BSIs due to *E. coli* (RR=1.82; 95% CI: 1.50-2.21; p<0.001) compared to those due to *K. pneumoniae* (RR=1.48; 95% CI: 1.17-1.87; p=0.001). Stratification by population age showed a higher RR in paediatric population (RR=2.09; 95% CI: 1.62-2.71; p<0.001). Effect estimates did not vary significantly by study country, mortality time assessment (14 vs 28 days), ESBL molecular resistance mechanisms, or study design (Figure 2 and online supplementary figure 3). Adjusted estimates for inappropriate empirical antibiotic therapy were provided for 14 studies. The pooled unadjusted OR for all-cause mortality was 2.91 (95% CI: 2.23-3.81; p<0.001, I^2=27.1%; p=0.164) and the pooled OR after adjusting for receipt of appropriate empirical treatment was 3.22 (95% CI: 1.53-6.76; p=0.002; I^2=87.5%; p<0.001).

Studies with non-invasive infections reported a RR of 1.58 (95% CI: 1.23-2.02; p<0.001) (supplementary figure 4).

Attributable mortality

Attributable mortality was analysed in 16 studies including 2,885 patients. All studies were performed in HICs. ESBL production in patients with BSIs increased the risk of attributable mortality by a factor of 1.75 (95% CI: 1.45-2.11; p<0.001; $I^{2=}$0%; p<0.001). The RR increased over time from 1.53 (95% CI: 1.10-2.12; p=0.011) in 1991-1999 to 1.91 (95% CI: 1.43-2.54; p<0.001) in 2000-2009 (Figure 3). Pathogen-specific RR for attributable mortality was 1.60 (95% CI: 1.18-2.15; p=0.002) for *K. pneumoniae* and 1.76 (95% CI: 1.33-2.34; p<0.001) when the gram-negative organisms were analysed all together without species differentiation. The subgroup analysis showed the RR was lower in case cohort studies (1.56; 95% CI: 1.09-2.25; p=0.016) than in cohort studies (1.80; 95% CI: 1.37-2.37; p<0.001).

Length of stay

LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive infections) analysing 38 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95% CI: 3.37-5.46; p<0.001) and decreased from 5.72 days (95% CI: 2.69-8.75; p<0.001) in 1991-1999 to 4.22 days (95% CI: 3.02-5.43; p<0.001) in 2000-2009 and was stable up to 2018 (4.30 days; 95% CI: 1.38-7.22; p=0,004). Higher WMD (p<0.001) was observed for BSIs due to *K. pneumoniae* (7.67 days; 4.63-10.71) than for those due to *E. coli* (6.07 days; 95% CI 3.71-8.43). Retrospective cohort studies reported higher (p<0.001) WMD (6.43 days; 95% CI: 4.66-8.21; p<0.001) than case cohort studies (3.32 days; 95% CI: 2.03-4.61). Studies in HICs showed higher WMD (4.56 days; 95% CI 3.43-5.70; p<0.001) than studies in LMICs (3.55 days; 95% CI 0.84-6.26; p=0.01) (Figure 4).

Studies with non-invasive infections reported a WMD of 2.19 days (95% CI: 1.56-2.81; p<0.001), which decreased from 7.66 (95% CI: 5.83-9.46; p<0.001) in 2000-2009 to 1.44 (95% CI: 0.77-2.10; p<0.001) in 2010-2018 (online supplementary figure 5).

The data on ICU-LOS were provided in 7 studies and showed that BSIs caused by ESBL producers had a WMD of LOS of 3.07 days (95% CI: 1.61-4.54; p<0.001).

Heterogeniety of the studied effect-modifiers did not reach statistical significance when assessed by metaregression (supplementary table S6).

Sensitivity analysis based on the quality of studies revealed no notable difference in the effect estimates after exclusion of low-quality studies (data not shown). Egger's test and the funnel plots (online supplementary figure 1 and 2) showed evidence for small study effects (p<0.001) and publication bias.

DISCUSSION

This systematic review shows that ESBL production has a significant impact on the most relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality, attributable mortality, and LOS both in hospital and in ICU were higher for patients with BSIs due to ESBL-producing *Enterobacteriaceae* than for patients with BSIs due to non-ESBL-producing strains. Non-invasive infections caused by ESBL-producing strains were associated with higher all-cause mortality and prolonged LOS. Within the limitation of the low number of studies evaluating specific patient populations, paediatric and cancer patients seemed to suffer a higher impact of ESBL invasive infections than the overall population. Stratifying by pathogen type, the impact of ESBL production was higher for *E. coli* BSIs than for *K. pneumoniae* BSIs. No relevant differences in mortality analysis emerged with stratification by study design or country income level. Impact of ESBL infections on mortality became more evident in more recent studies. Studies reporting on appropriateness of empirical therapy, ESBL resistance mechanisms, and MICs showed a higher clinical impact of ESBL infections than studies not assessing these variables. In particular, pooled ORs adjusted for inappropriate empirical treatment, showed a remarkably higher OR for mortality in patients with ESBL infections.

Our findings confirm the results of previous systematic reviews. Schwaber et al. performed a systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies published through 2003.[2] The authors show a pooled RR for all-cause mortality of 1.85 but, in contrast to our study, they combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in the analysis because of sample size limitations. Rottier et al. analysed studies published through 2010 and adjusting results for inappropriate empirical treatment found an adjusted OR of 1.37.[3] Our study, adding more than 50 studies in 17 years to the Rottier systematic review, confirmed the clinical importance of ESBL production to all-cause mortality and for the first time assessed the role of ESBL production on attributable mortality. We addressed relevant effect-modifiers through subgroup analyses and found that population, pathogen, and assessment of empiric therapy all had an impact on estimates. Because we believe that appropriate empirical treatment plays a relevant role in invasive infections, we performed a secondary analysis by pooling only adjusted ORs and confirming the significant impact of antibiotic resistance as already shown in a previously published systematic review.[96] The lack of consideration of appropriateness of therapy in the studies evaluating mortality seems to underestimate the risk of ESBL production on mortality. However, studies assessing the impact of appropriate therapy did not provide

homogeneous definition and could refer either to empirical or definite therapy or a single component irrespective of the dosage, making results difficult to interpret. The impact of ESBL production on LOS has been also estimated, assessing BSIs and non-invasive infections separately and confirming the prolongation of hospitalisation.

Our systematic review contributes to the discussion on the limitation of current evidence for the estimation of mortality due to antibiotic-resistant infections. Our finding underlines the importance of considering a multivariable model with a whole set of determinants when trying to quantify the impact of resistance on clinical outcomes. The source of infection, for example, can influence the role of empirical treatment on the clinical outcome. For example, patients with UTI receiving inappropriate empirical antibiotic therapy can potentially show a favourable outcome, most probably due to the high concentration of antibiotic reached in the urinary tract.[97]

Our study has some limitations. Although results of the meta-analyses were significant in all the subgroups, we could analyse only a limited number of studies providing information for subgroups such as haematological patients and low-income countries, making generalizability of results less certain for these specific patient populations. Only a few studies reported MIC data or specific ESBL molecular resistant phenotype (i.e., AmpC). Moreover, publication bias was detected in both the main analyses (all-cause mortality and LOS), thus implying the possibility that results from small studies with non-significant results might have been conducted and not published, resulting in a possible overestimation of our results. The non-homogeneous reporting of some relevant data in published literature (e.g., disease severity, underlying comorbidities and resistance mechanism) may also have affected the precision of the estimate. Patients with ESBL are intrinsically at higher risk of mortality and complications because they are often older, have more comorbidities or higher antibiotic exposure, and are at higher risk of receiving inappropriate empirical treatment.[98] Finally, due to resource constraints, we had to limit our search to PubMed database with the chance of missing relevant studies.

In summary, our systematic review emphasises the importance of suspicion and confirmation of ESBL production as soon as possible for invasive infections and demonstrates that ESBL production increases the risk of attributable mortality and LOS in both hospital and ICU for invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of mortality and prolonged LOS even after adjustment for empiric inappropriate treatment. Control for other relevant effect-modifiers is hindered by the sparseness of published data. Future studies addressing the clinical burden of drug-resistant infections must include ESBL

production and should assess both the impact of molecular mechanisms of resistance and effect on specific patient populations such as haematological patients and those in LMIC.

Acknowledgements We thank Anne McDonough, a professional medical writer who provided medical writing support funded by the authors.

Author Contributions ET contributed to the study concept. BPG and PS performed data analysis. PS and AC extracted data and wrote the first draft of the manuscript. DL contributed to the first draft of the manuscript. EC and ET wrote the final version of the manuscript. CB reviewed the paper. All authors read, edited, and approved the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding This work was supported by the German Center for Infection Research Clinical Research Unit for Health-Care Associated Infections grant number TTU 08.701 and DRIVE-AB (115618). The funder had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Competing interests The authors report no competing interests.

Patient consent Not required

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Requests for data should be addressed to the corresponding author.

REFERENCES

1. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 2018;18:318–27.
2. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:913–20.
3. Rottier WC, Ammerlaan HS, Bonten MJ. Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. *J Antimicrob Chemother* 2012;67:1311–20.
4. Cassini A, Högberg LD, Plachouras D, et al; Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;19:56–66.
5. The World Bank. What is the World Bank Atlas method? https://datahelpdesk.worldbank.org/knowledgebase/articles/77933-what-is-the-world-bank-atlas-method. Accessed January 14, 2019.
6. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M *et al*. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. The Ottawa Health Research Institute: Ottawa, Canada. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed April 14 2015
7. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
9. Lautenbach E, Patel JB, Bilker WB, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *Clin Infect Dis* 2001;32:1162–71.
10. Leistner R, Sakellariou C, Gurntke S, et al. Mortality and molecular epidemiology associated with extended-spectrum beta-lactamase production in Escherichia coli from bloodstream infection. *Infect Drug Resist* 2014;7:57–62.

11. Lin JN, Chen YH, Chang LL, et al. Clinical characteristics and outcomes of patients with extended-spectrum beta-lactamase-producing bacteremias in the emergency department. *Intern Emerg Med* 2011;6:547–55.
12. Kim HJ, Park JH, Park DI, et al. Clinical impact of extended-spectrum beta-lactamase-producing Enterobacteriaceae in patients with biliary tract infection. *Dig Dis Sci* 2013;58:841–9.
13. Kim SH, Kwon JC, Choi SM, et al. Escherichia coli and Klebsiella pneumoniae bacteremia in patients with neutropenic fever: factors associated with extended-spectrum beta-lactamase production and its impact on outcome. *Ann Hematol* 2013;92:533–41.
14. Pillay T, Pillay DG, Adhikari M, et al. Piperacillin/tazobactam in the treatment of Klebsiella pneumoniae infections in neonates. *Am J Perinatol* 1998;15:47–51.
15. Kim BN, Woo JH, Kim MN, et al. Clinical implications of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae bacteraemia. *J Hosp Infect* 2002;52:99–106.
16. Kim YK, Pai H, Lee HJ, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in children: epidemiology and clinical outcome. *Antimicrob Agents Chemother* 2002;46:1481–91.
17. Bhavnani SM, Ambrose PG, Craig WA, et al. Outcomes evaluation of patients with ESBL- and non-ESBL-producing Escherichia coli and Klebsiella species as defined by CLSI reference methods: report from the SENTRY Antimicrobial Surveillance Program. *Diagn Microbiol Infect Dis* 2006;54:231–6.
18. Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol* 2005;43:745–9.
19. Panhotra BR, Saxena AK, Al-Ghamdi AM. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae hospital acquired bacteremia. Risk factors and clinical outcome. *Saudi Med J* 2004;25:1871–6.
20. Marra AR, Wey SB, Castelo A, et al. Nosocomial bloodstream infections caused by Klebsiella pneumoniae: impact of extended-spectrum beta-lactamase (ESBL) production on clinical outcome in a hospital with high ESBL prevalence. *BMC Infect Dis* 2006;6:24.
21. Skippen I, Shemko M, Turton J, et al. Epidemiology of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp.: a nested case-control study from a tertiary hospital in London. *J Hosp Infect* 2006;64:115–23.

22. Schwaber MJ, Navon-Venezia S, Kaye KS, et al. Clinical and economic impact of bacteremia with extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2006;50:1257–62.
23. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Clinical and molecular epidemiology of community-onset, extended-spectrum beta-lactamase-producing Escherichia coli infections in Thailand: a case-case-control study. *Am J Infect Control* 2007;35:606–12.
24. Tumbarello M, Spanu T, Sanguinetti M, et al. Bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae: risk factors, molecular epidemiology, and clinical outcome. *Antimicrob Agents Chemother* 2006;50:498–504.
25. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Risk factors for and outcomes of healthcare-associated infection due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae in Thailand. *Infect Control Hosp Epidemiol* 2007;28:873–6. doi: 10.1086/518725
26. Kanafani ZA, Mehio-Sibai A, Araj GF, et al. Epidemiology and risk factors for extended-spectrum beta-lactamase-producing organisms: a case control study at a tertiary care center in Lebanon. *Am J Infect Control* 2005;33:326–32.
27. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in children. *Pediatrics* 2005;115:942–9.
28. Loh LC, Nor Izran Hanim Bt Abdul S, Rosdara Masayuni Bt Mohd S, et al. Hospital Outcomes of Adult Respiratory Tract Infections with Extended-Spectrum B-Lactamase (ESBL) Producing Klebsiella Pneumoniae. *Malays J Med Sci* 2007;14:36–40.
29. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing E. coli compared to non-ESBL producing E. coli. *J Infect* 2007;55:254–9. doi: 10.1016/j.jinf.2007.04.007
30. Song KH, Jeon JH, Park WB, et al. Clinical outcomes of spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species: a retrospective matched case-control study. *BMC Infect Dis* 2009;9:41.
31. Bennett JW, Robertson JL, Hospenthal DR, et al. Impact of extended spectrum beta-lactamase producing Klebsiella pneumoniae infections in severely burned patients. *J Am Coll Surg* 2010;211:391–9.
32. Trecarichi EM, Tumbarello M, Spanu T, et al. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream

infections caused by Escherichia coli in patients with hematological malignancies. *J Infect* 2009;58:299–307.

33. Tuon FF, Kruger M, Terreri M, et al. Klebsiella ESBL bacteremia-mortality and risk factors. *Braz J Infect Dis* 2011;15:594–8.
34. Kang CI, Song JH, Chung DR, et al. Risk factors and treatment outcomes of community-onset bacteraemia caused by extended-spectrum beta-lactamase-producing Escherichia coli. *Int J Antimicrob Agents* 2010;36:284–7.
35. Pena C, Gudiol C, Calatayud L, et al. Infections due to Escherichia coli producing extended-spectrum beta-lactamase among hospitalised patients: factors influencing mortality. *J Hosp Infect* 2008;68:116–22.
36. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. *Antimicrob Agents Chemother* 2010;54:4085–91.
37. Kang CI, Chung DR, Ko KS, et al. Risk factors for infection and treatment outcome of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in patients with hematologic malignancy. *Ann Hematol* 2012;91:115–21.
38. Wu YH, Chen PL, Hung YP, et al. Risk factors and clinical impact of levofloxacin or cefazolin nonsusceptibility or ESBL production among uropathogens in adults with community-onset urinary tract infections. *J Microbiol Immunol Infect* 2014;47:197–203.
39. Rodriguez-Bano J, Picon E, Gijon P, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli: risk factors and prognosis. *Clin Infect Dis* 2010;50:40–8.
40. Gurntke S, Kohler C, Steinmetz I, et al. Molecular epidemiology of extended-spectrum beta-lactamase (ESBL)-positive Klebsiella pneumoniae from bloodstream infections and risk factors for mortality. *J Infect Chemother* 2014;20:817–9.
41. Oh MM, Chae JY, Kim JW, et al. Positive culture for extended-spectrum beta-lactamase during acute prostatitis after prostate biopsy is a risk factor for progression to chronic prostatitis. *Urology* 2013;81:1209–12.
42. Leistner R, Gurntke S, Sakellariou C, et al. Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive K. pneumoniae and E. coli: an analysis of the disease burden in a large cohort. *Infection* 2014;42:991–7.
43. Ku NS, Chung HS, Choi JY, et al. Clinical usefulness of the 2010 clinical and laboratory standards institute revised breakpoints for cephalosporin use in the treatment of bacteremia caused by Escherichia coli or Klebsiella spp. *Biomed Res Int* 2015;2015:831074.

44. Anunnatsiri S, Towiwat P, Chaimanee P. Risk factors and clinical outcomes of extended spectrum beta-lactamase (ESBL)-producing Escherichia coli septicemia at Srinagarind University Hospital, Thailand. *Southeast Asian J Trop Med Public Health* 2012;43:1169–77.
45. Kang CI, Kim SH, Kim DM, et al. Risk factors for and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae. *Infect Control Hosp Epidemiol* 2004;25:860–7.
46. Raviv Y, Shitrit D, Amital A, et al. Multidrug-resistant Klebsiella pneumoniae acquisition in lung transplant recipients. *Clin Transplant* 2012;26:E388–94.
47. MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. *J Hosp Med* 2014;9:232–8.
48. Abhilash KP, Veeraraghavan B, Abraham OC. Epidemiology and outcome of bacteremia caused by extended spectrum beta-lactamase (ESBL)-producing Escherichia coli and Klebsiella spp. in a tertiary care teaching hospital in south India. *J Assoc Physicians India* 2010;58 Suppl:13-7.
49. Shanthi M, Sekar U. Extended spectrum beta lactamase producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *J Assoc Physicians India* 2010;58 Suppl:41–4.
50. Han SB, Jung SW, Bae EY, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in febrile neutropenic children. *Microb Drug Resist* 2015;21:244–51.
51. Lee S, Song DY, Cho SH, et al. Impact of extended-spectrum beta-lactamase on acute pyelonephritis treated with empirical ceftriaxone. *Microb Drug Resist* 2014;20:39–44.
52. Chayakulkeeree M, Junsriwong P, Keerasuntonpong A, et al. Epidemiology of extended-spectrum beta-lactamase producing gram-negative bacilli at Siriraj Hospital, Thailand, 2003. *Southeast Asian J Trop Med Public Health* 2005;36:1503–9.
53. Apisarnthanarak A, Kiratisin P, Mundy LM. Predictors of mortality from community-onset bloodstream infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. *Infect Control Hosp Epidemiol* 2008;29:671–4.
54. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Predictors of mortality among patients with community-onset infection due to extended-spectrum beta-lactamase-producing Escherichia coli in Thailand. *Infect Control Hosp Epidemiol* 2008;29:80–2.

55. Jean SS, Ko WC, Xie Y, et al. Clinical characteristics of patients with community-acquired complicated intra-abdominal infections: a prospective, multicentre, observational study. *Int J Antimicrob Agents* 2014;44:222–8.
56. Lee J, Pai H, Kim YK, et al. Control of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a children's hospital by changing antimicrobial agent usage policy. *J Antimicrob Chemother* 2007;60:629–37.
57. Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, et al. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. *Int J Clin Pract* 2012;66:891–6.
58. Ha YE, Kang CI, Cha MK, et al. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in patients with cancer. *Int J Antimicrob Agents* 2013;42:403–9.
59. Du B, Long Y, Liu H, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bloodstream infection: risk factors and clinical outcome. *Intensive Care Med* 2002;28:1718–23.
60. Stone PW, Gupta A, Loughrey M, et al. Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae outbreak in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2003;24:601–6.
61. Pena C, Pujol M, Ardanuy C, et al. An outbreak of hospital-acquired Klebsiella pneumoniae bacteraemia, including strains producing extended-spectrum beta-lactamase. *J Hosp Infect* 2001;47:53–9.
62. Kola A, Maciejewski O, Sohr D, et al. Clinical impact of infections caused by ESBL-producing E. coli and K. pneumoniae. *Scand J Infect Dis* 2007;39:975–82.
63. Tsai MH, Lee IT, Chu SM, et al. Clinical and Molecular Characteristics of Neonatal Extended-Spectrum beta-Lactamase-Producing Gram-Negative Bacteremia: A 12-Year Case-Control-Control Study of a Referral Center in Taiwan. *PLoS One* 2016;11(8):e0159744.
64. Maslikowska JA, Walker SA, Elligsen M, et al. Impact of infection with extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella species on outcome and hospitalization costs. *J Hosp Infect* 2016;92:33–41.
65. Onken A, Said AK, Jorstad M, et al. Prevalence and antimicrobial resistance of microbes causing bloodstream infections in Unguja, Zanzibar. *PLoS One* 2015;10:e0145632.
66. Nguyen ML, Toye B, Kanji S, et al. Risk factors for and outcomes of bacteremia caused by extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella species at a

Canadian tertiary care hospital. *Can J Hosp Pharm* 2015;68(2):136–43. [published Online First: 2015/05/13]

67. Denis B, Lafaurie M, Donay JL, et al. Prevalence, risk factors, and impact on clinical outcome of extended-spectrum beta-lactamase-producing Escherichia coli bacteraemia: a five-year study. Int *J Infect Dis* 2015;39:1–6.
68. Chopra T, Marchaim D, Johnson PC, et al. Risk factors for bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: A focus on antimicrobials including cefepime. *Am J Infect Control* 2015;43:719–23.
69. Artero A, Esparcia A, Alberola J, et al. Prospective cohort study of risk factors for extended-spectrum ss-lactamase-producing Escherichia coli urinary tract infections in elderly patients admitted to hospital. *Int J Clin Pract* 2017;71:doi:10.1111/ijcp.13001
70. Chen IL, Huang HC, Wu CT, et al. Analysis of early-onset bloodstream infection due to Escherichia coli infection in premature babies. *Medicine* 2017;96:e7748.
71. Islas-Munoz B, Volkow-Fernandez P, Ibanes-Gutierrez C, et al. Bloodstream infections in cancer patients. Risk factors associated with mortality. *Int J Infect Dis* 2018;71:59–64.
72. Ma J, Li N, Liu Y, et al. Antimicrobial resistance patterns, clinical features, and risk factors for septic shock and death of nosocomial E coli bacteremia in adult patients with hematological disease: A monocenter retrospective study in China. *Medicine* 2017;96:e6959.
73. Man MY, Shum HP, Chan YH, et al. Clinical predictors and outcomes of Klebsiella pneumoniae bacteraemia in a regional hospital in Hong Kong. *J Hosp Infect* 2017;97:35–41.
74. Marando R, Seni J, Mirambo MM, et al. Predictors of the extended-spectrum-beta lactamases producing Enterobacteriaceae neonatal sepsis at a tertiary hospital, Tanzania. *Int J Med Microbiol* 2018;308:803–11.
75. Namikawa H, Yamada K, Fujimoto H, et al. Clinical characteristics of bacteremia caused by extended-spectrum beta-lactamase-producing Escherichia coli at a tertiary hospital. *Intern Med* 2017;56:1807–15.
76. Shi SH, Feng XN, Lai MC, et al. Biliary diseases as main causes of pyogenic liver abscess caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Liver Int* 2017;37:727–34.

77. Tanir Basaranoglu S, Ozsurekci Y, Aykac K, et al. A comparison of blood stream infections with extended spectrum beta-lactamase-producing and non-producing Klebsiella pneumoniae in pediatric patients. *Ital J Pediat* 2017;43:79.
78. Razazi K, Mekontso Dessap A, Carteaux G, et al. Frequency, associated factors and outcome of multi-drug-resistant intensive care unit-acquired pneumonia among patients colonized with extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Ann Intensive Care* 2017;7:61.
79. Ray S, Anand D, Purwar S, et al. Association of high mortality with extended-spectrum beta-lactamase (ESBL) positive cultures in community acquired infections. *J Crit Care* 2018;44:255–60.
80. Haruki Y, Hagiya H, Haruki M, et al. Clinical characteristics and outcome of critically ill patients with bacteremia caused by extended-spectrum beta-lactamase-producing and non-producing Escherichia coli. *J Infect Chemother* 2018;24:944–7.
81. Lin WT, Tang HJ, Lai CC, et al. Clinical manifestations and bacteriological features of culture-proven Gram-negative bacterial arthritis. *J Microbiol Immunol Infect* 2017;50:527–31.
82. Buys H, Muloiwa R, Bamford C, et al. Klebsiella pneumoniae bloodstream infections at a South African children's hospital 2006-2011, a cross-sectional study. BMC Infect Dis 2016;16:570.
83. Lee CC, Lee CH, Hong MY, et al. Propensity-matched analysis of the impact of extended-spectrum beta-lactamase production on adults with community-onset Escherichia coli, Klebsiella species, and Proteus mirabilis bacteremia. *J Microbiol Immunol Infect* 2018;51:519–26.
84. Huang YY, Alleyne A, Leung V, et al. Urosepsis due to extended-ppectrum beta-lactamase-producing Escherichia coli: a retrospective, single-centre review of risk Factors and clinical outcomes. *Can J Hosp Pharm* 2018;71:119-27.
85. Komatsu Y, Kasahara K, Inoue T, et al. Molecular epidemiology and clinical features of extended-spectrum beta-lactamase- or carbapenemase-producing Escherichia coli bacteremia in Japan. *PLoS One* 2018;13:e0202276.
86. Liu M, Li M, Wu L, et al. Extended-spectrum beta-lactamase-producing E. coli septicemia among rectal carriers in the ICU. *Medicine* 2018;97:e12445.
87. Nivesvivat T, Piyaraj P, Thunyaharn S, et al. Clinical epidemiology, risk factors and treatment outcomes of extended-spectrum beta-lactamase producing Enterobacteriaceae

bacteremia among children in a tertiary care hospital, Bangkok, Thailand. *BMC Res Notes* 2018;11:624.

88. Cordery RJ, Roberts CH, Cooper SJ, et al. Evaluation of risk factors for the acquisition of bloodstream infections with extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in the intensive care unit; antibiotic management and clinical outcome. *J Hosp Infect* 2008;68:108–15.
89. Daikos GL, Kosmidis C, Tassios PT, et al. Enterobacteriaceae bloodstream infections: presence of integrons, risk factors, and outcome. *Antimicrob Agents Chemother* 2007;51:2366–72. doi: 10.1128/AAC.00044-07 [published Online First: 2007/04/25]
90. Gudiol C, Calatayud L, Garcia-Vidal C, et al. Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. *J Antimicrob Chemother* 2010;65(2):333–41.
91. Marchaim D, Gottesman T, Schwartz O, et al. National multicenter study of predictors and outcomes of bacteremia upon hospital admission caused by Enterobacteriaceae producing extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2010;54:5099–104.
92. Menashe G, Borer A, Yagupsky P, et al. Clinical significance and impact on mortality of extended-spectrum beta lactamase-producing Enterobacteriaceae isolates in nosocomial bacteremia. *Scand J Infect Dis* 2001;33:188–93.
93. Ortega M, Marco F, Soriano A, et al. Analysis of 4758 Escherichia coli bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. *J Antimicrob Chemother* 2009;63:568–74.
94. Szilagyi E, Fuzi M, Borocz K, et al. Risk factors and outcomes for bloodstream infections with extended-spectrum beta-lactamase-producing Klebsiella pneumoniae ; Findings of the nosocomial surveillance system in Hungary. *Acta Microbiol Immunol Hung* 2009;56:251–62. doi:
95. Tsai SS, Huang JC, Chen ST, et al. Characteristics of Klebsiella pneumoniae bacteremia in community-acquired and nosocomial infections in diabetic patients. *Chang Gung Med J* 2010;33:532–9.
96. Carrara E, Pfeffer I, Zusman O, et al. Determinants of inappropriate empirical antibiotic treatment: systematic review and meta-analysis. *Int J Antimicrob Agents* 2018;51:548–53,
97. Horcajada JP, Shaw E, Padilla B, et al. Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective

multicentre cohort study in the era of antimicrobial resistance. *Clin Microbiol Infect*. 2013 Oct;19(10):96

98. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clin Microbiol Infect* 2014;20:973–80.

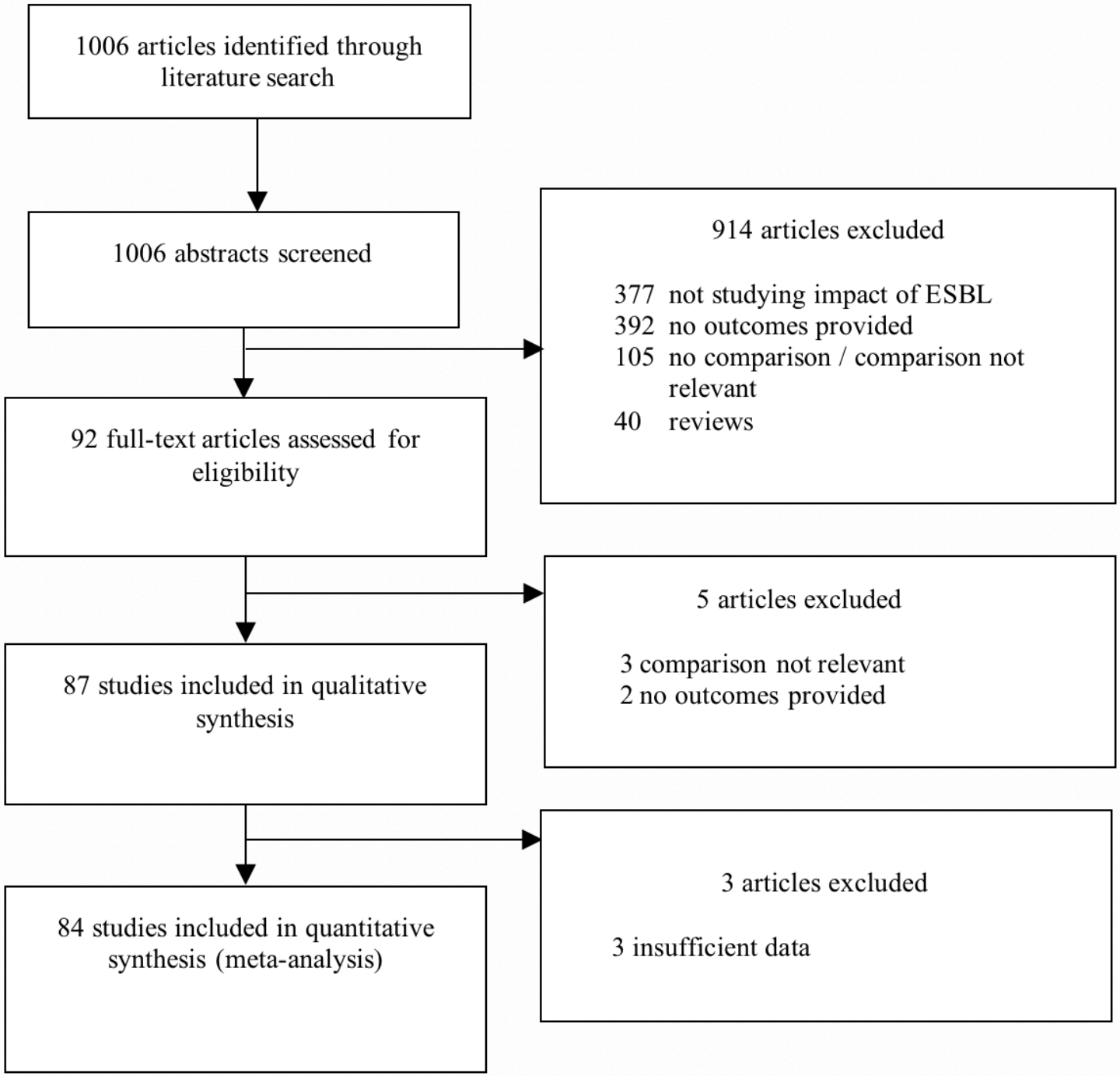
FIGURE LEGENDS

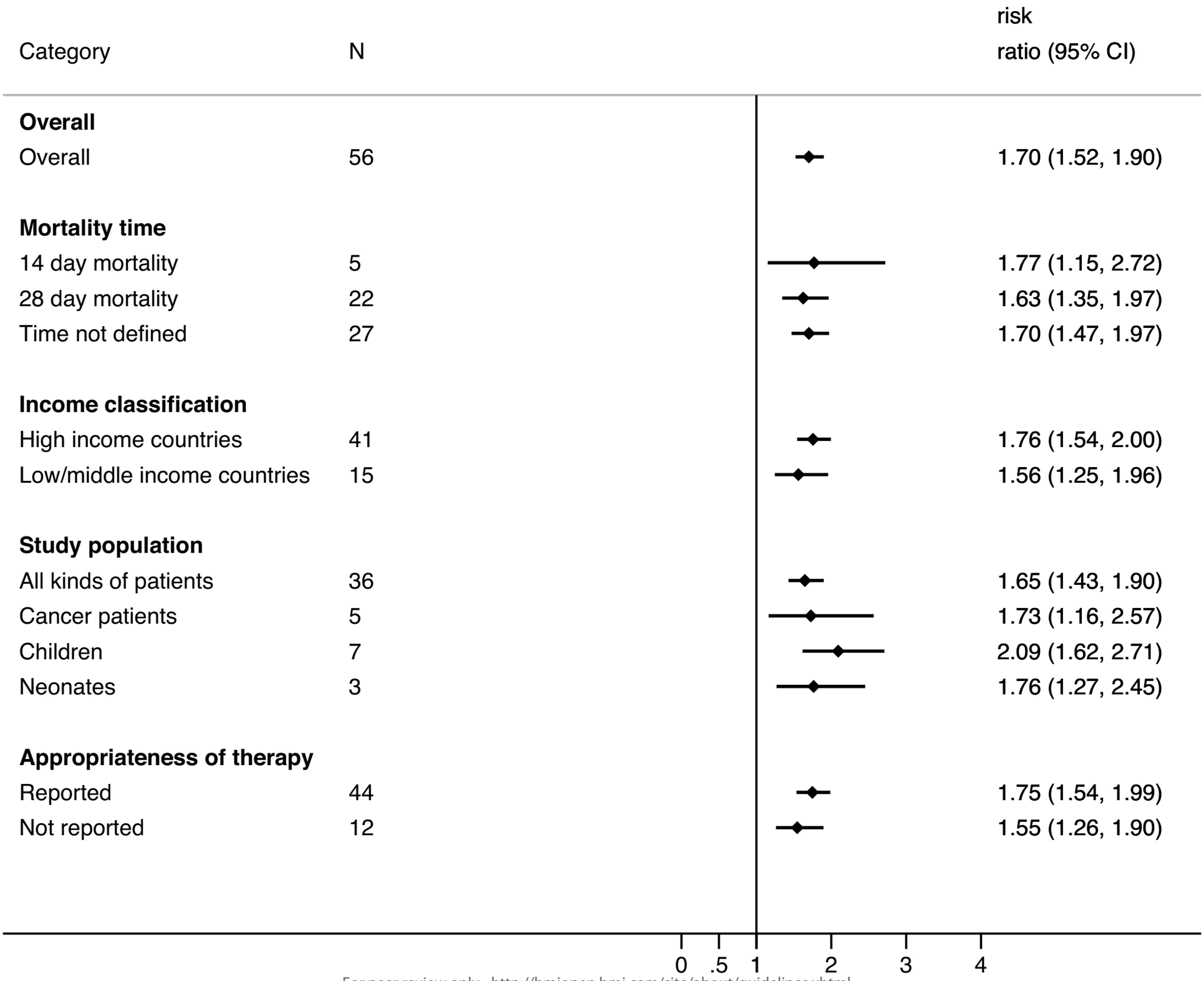
Figure 1: Literature search and study inclusion and exclusion

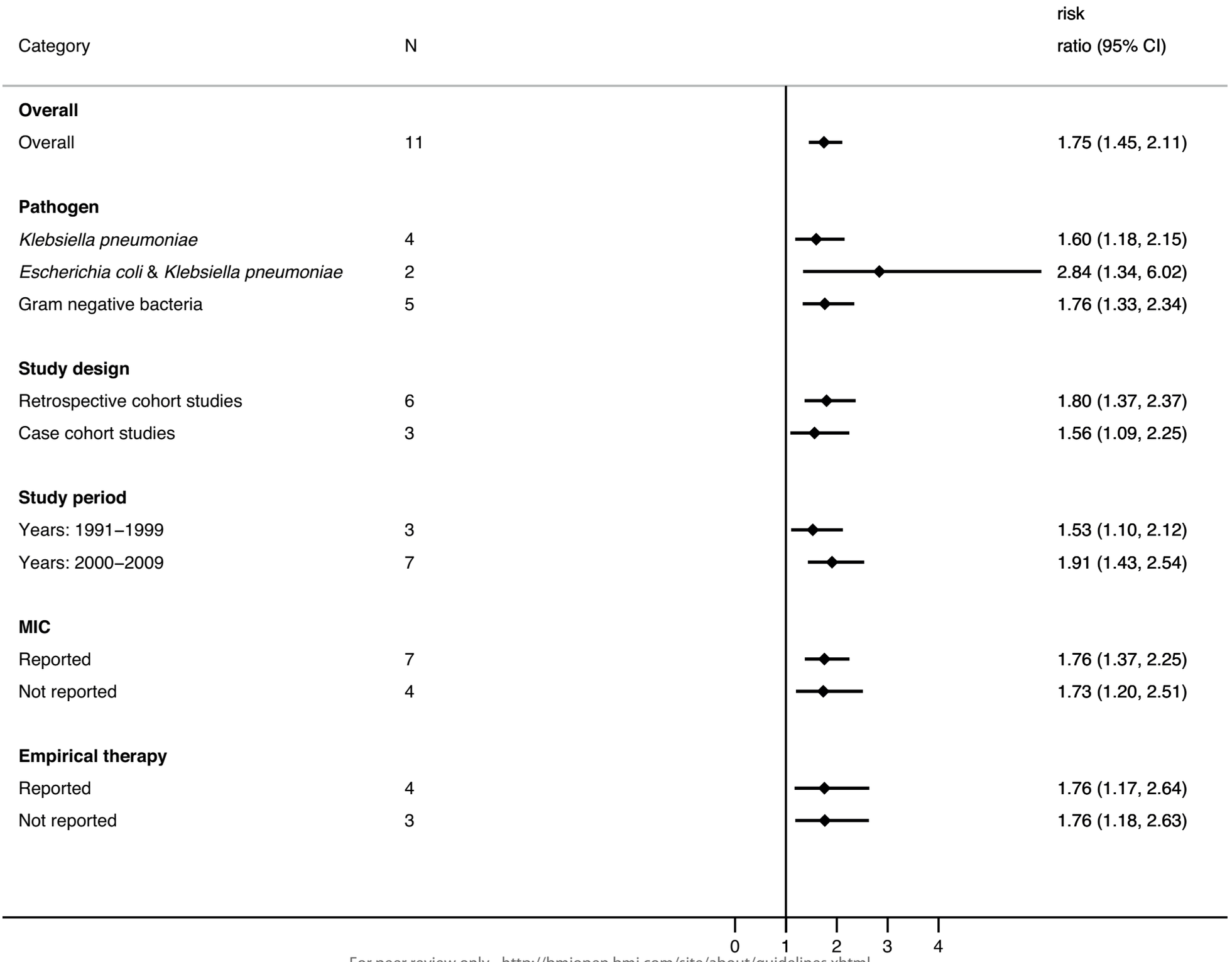
Figure 2: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections— subgroups not included in attributable mortality

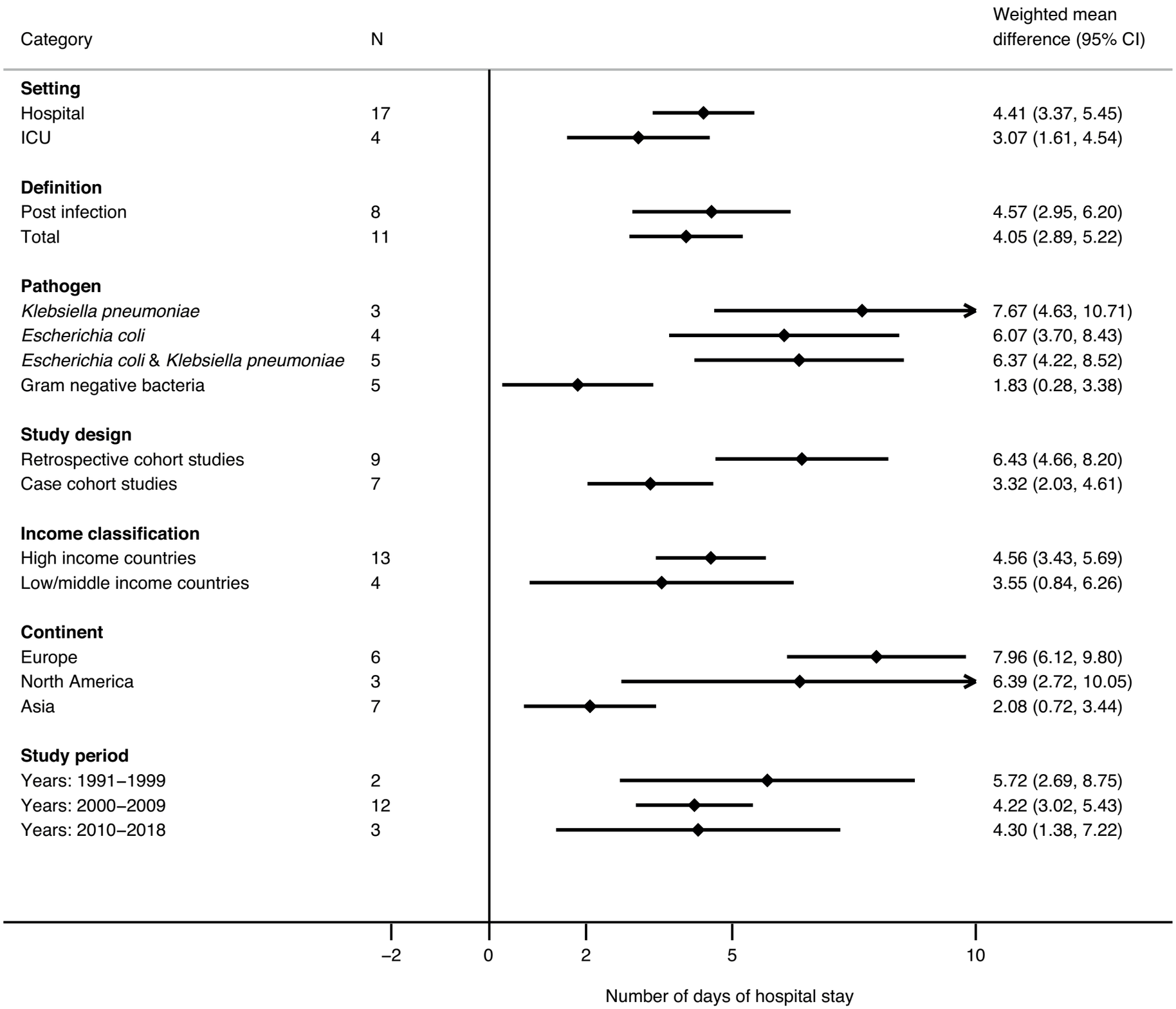
Figure 3: Pooled risk ratios for attributable mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

Figure 4: Weighted mean difference in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

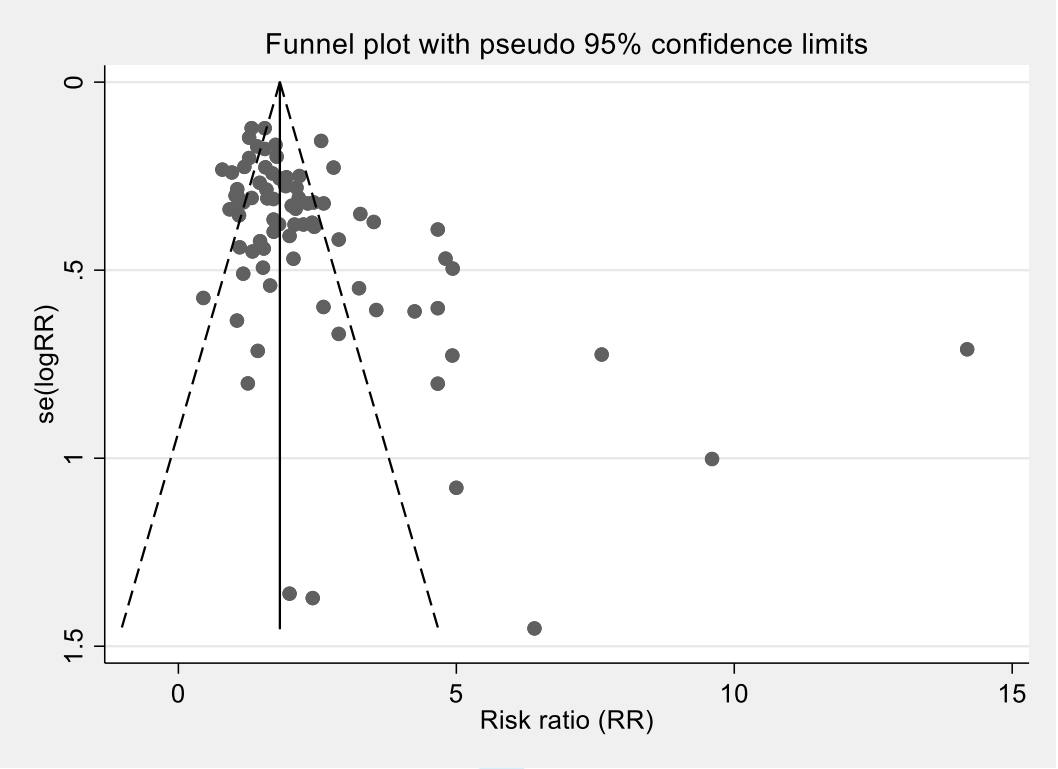

1006 articles identified through literature search
1006 abstracts screened
914 articles excluded
377 not studying impact of ESBL
392 no outcomes provided
105 no comparison / comparison not relevant
40 reviews
92 full-text articles assessed for eligibility
5 articles excluded
3 comparison not relevant
2 no outcomes provided
87 studies included in qualitative synthesis
3 articles excluded
3 insufficient data
84 studies included in quantitative synthesis (meta-analysis)





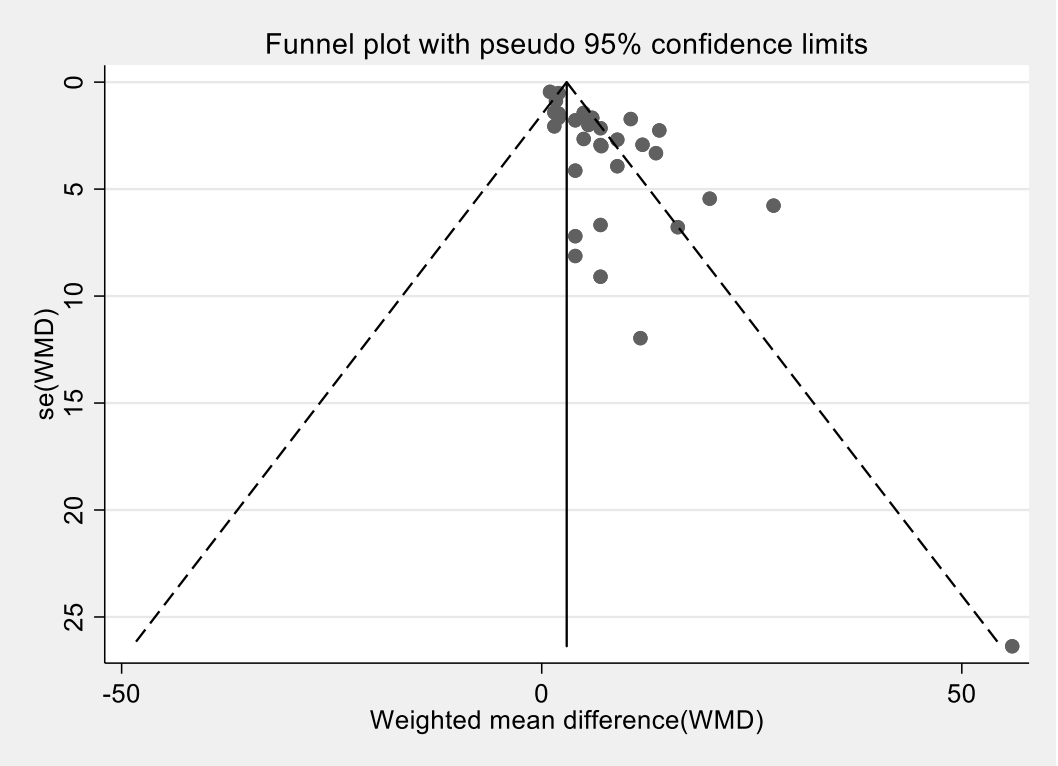

Category
N
Weighted mean difference (95% CI)
Setting
Hospital 17 4.41 (3.37, 5.45)
ICU 4 3.07 (1.61, 4.54)
Definition
Post infection 8 4.57 (2.95, 6.20)
Total 11 4.05 (2.89, 5.22)
Pathogen
Klebsiella pneumoniae 3 7.67 (4.63, 10.71)
Escherichia coli 4 6.07 (3.70, 8.43)
Escherichia coli & Klebsiella pneumoniae 5 6.37 (4.22, 8.52)
Gram negative bacteria 5 1.83 (0.28, 3.38)
Study design
Retrospective cohort studies 9 6.43 (4.66, 8.20)
Case cohort studies 7 3.32 (2.03, 4.61)
Income classification
High income countries 13 4.56 (3.43, 5.69)
Low/middle income countries 4 3.55 (0.84, 6.26)
Continent
Europe 6 7.96 (6.12, 9.80)
North America 3 6.39 (2.72, 10.05)
Asia 7 2.08 (0.72, 3.44)
Study period
Years: 1991–1999 2 5.72 (2.69, 8.75)
Years: 2000–2009 12 4.22 (3.02, 5.43)
Years: 2010–2018 3 4.30 (1.38, 7.22)
−2
0
2
5
10
Number of days of hospital stay

Supplementary figure 1: Funnel plot of risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



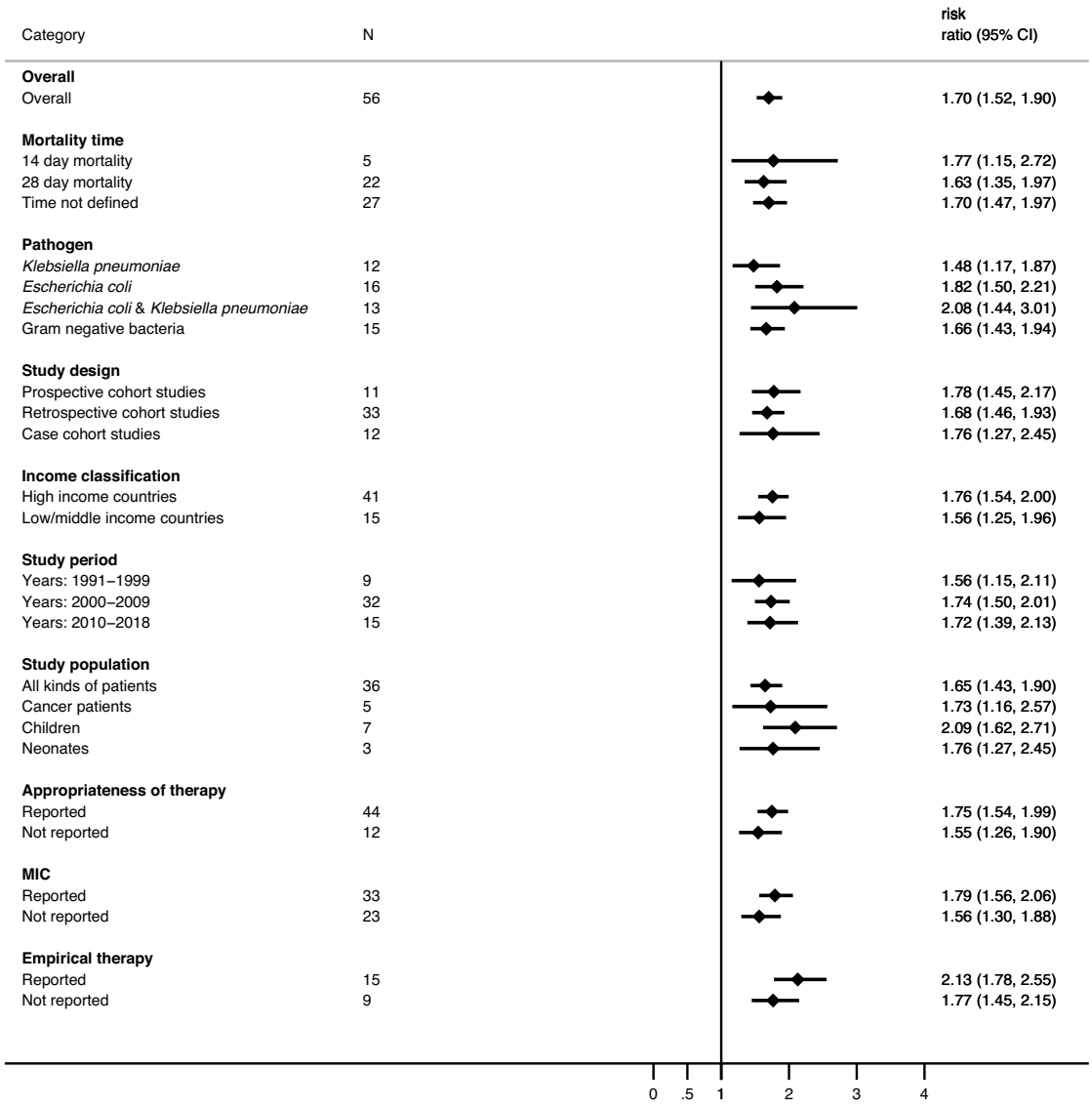
The y axis se(logRR) is the standard error of the log risk ratio Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 2: Funnel plot of weighted mean differences in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

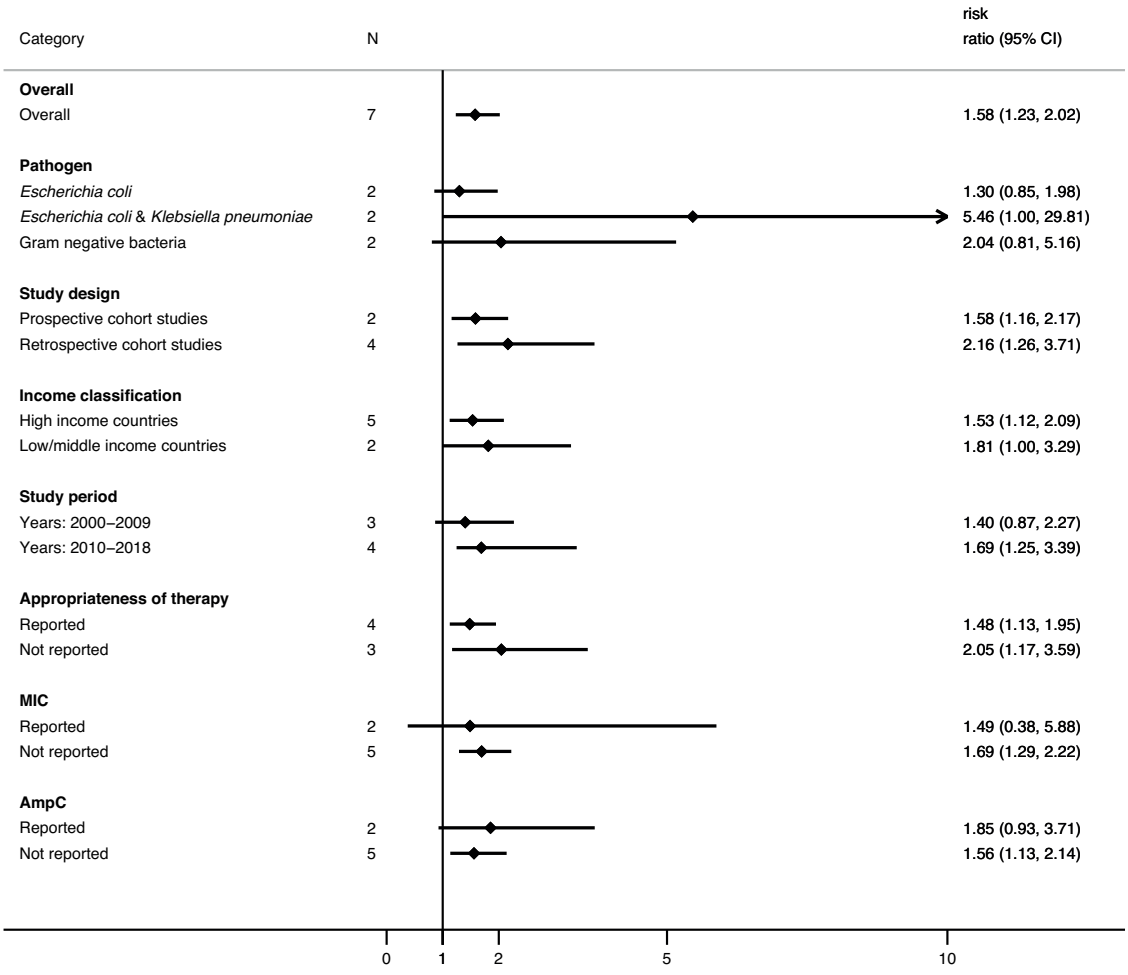


The y axis se(WMD) is the standard error of the weighted mean difference. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

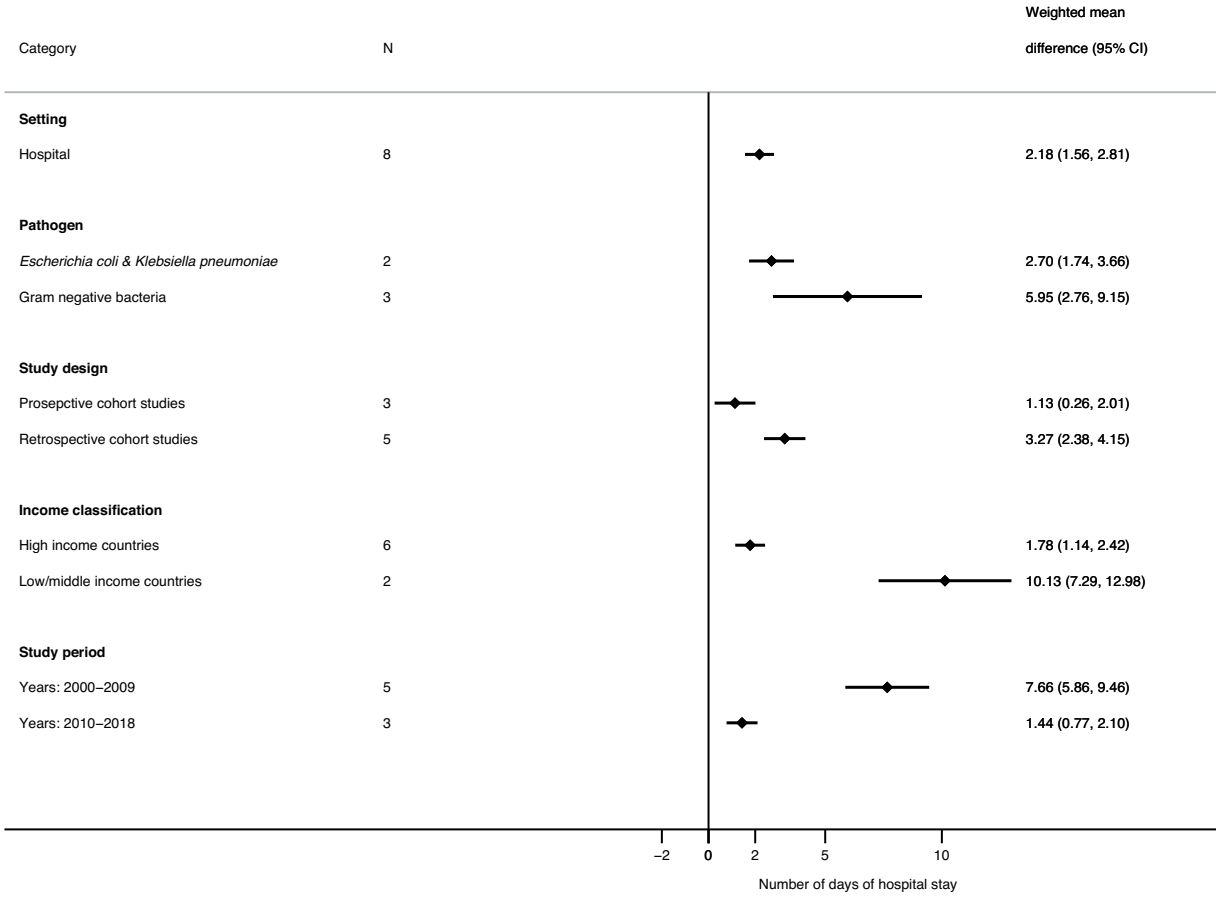
Supplementary figure 3: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections—all subgroups



Supplementary figure 4: Pooled risk ratios for all-cause mortality in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary figure 5: Weighted mean differences in length of hospital stay in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary table S1: Search terms used in PubMed :

((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh])

AND

(Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])) OR (Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])

Coupled with

(length of stay[mesh] OR (hospitalisation[tw] AND length[tw]) OR length of hospitalisation[tw] OR length of hospitalization[tw] OR duration of hospitalization[tw] duration of hospitalisation[tw] OR LOS[tw] OR ((period[tw] OR length[tw]) AND (hospital stay[tw] OR hospitalisation[tw] OR hospitalization[tw]) OR

(mortality[mesh] OR mortality[tw] OR death rate[tw] OR fatality[tw] OR survival rate[tw] OR death[tw] OR died[tw] OR dead[tw])))) OR

(cost[Title/Abstract] OR"costs and cost analysis"[MeSH:noexp])*

Coupled with

("0001/01/01"[PDat] : "2018/10/01"[PDat]))

Supplementary table S2: Modified Newcastle Ottawa quality assessment scale for case-control studies and cohort studies.

	For case cohort studies, the quality criteria assessed are		
1	**Is the case definition adequate?**	a*	yes, with independent validation
		b	yes, eg. record linkage or based on self-report
		c	no description
2	**Representativeness of the cases**	a*	consecutive or obviously representative series of cases
		b	potential for selection biases or not stated
3	**Selection of Controls**	a*	community controls
		b	hospital controls
		c	no description
4	**Definition of Controls**	a*	no history of disease (endpoint)
		b	no description of source
5	**Comparability of cases and controls on the basis of the design or analysis**	a*	study controls for at least one variable (including age, sex and comorbidities)
		b**	study controls for more than one variable (including age, sex and comorbidities)
6	**Ascertainment of exposure**	a*	secure record (eg surgical records)
		b	structured interview blind to case/control status
		c	interview not blinded to case/control status
		d	written self-report or medical record only
		e	no description
7	**Same method of ascertainment for cases and controls**	a*	yes
		b	no
		c	unclear
8	**Non-Response rate**	a	same rate for both groups
		b	non respondents described
		c	rate different and no designation
	For cohort studies, the quality criteria assessed are		
1	**Representativeness of the exposed cohort**	a*	truly representative
		b*	somewhat representative
		c	selected group of users
		d	no description
2	**Selection of the non-exposed cohort**	a*	drawn from the same community as the exposed cohort
		b	drawn from a different source
		c	no description of the derivation of the non-exposed cohort
3	**Ascertainment of exposure**	a*	secure record (eg surgical records)
		a*	structured interview
		c	written self-report
		d	no description
4	**Demonstration that outcome of interest was not present at start of study**	a*	yes
		b	no
		c	unclear
5	**Comparability of cohorts on the basis of the design or analysis**	a*	study controls for age or comorbidities
		b**	study controls for age and comorbidities
6	**Assessment of outcome:**	a*	independent blind assessment
		b*	record linkage
		c	self-report
		d	no description

7	**Follow-up long enough for outcomes to occur**	a*	yes
		b	no
		c	unclear
8	**Adequacy of follow up of cohorts**	a*	complete follow up – all that matters subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number
		b*	inadequate numbers but description provided of those lost
		c	inadequate follow up rate and no description of those lost
		d	no statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Supplementary table S3: Study characteristics overview

Subgroup	All Studies	Bloodstream infections	Noninvasive infections
	87	**57**	**10**
Country			
South Korea [11,12,14,15,29,33,36,40,42,44,49,50,55,57]	14	9	2
Thailand [22,24,43,51-53,86]	7	3	
USA [8,16,26,30,46,59,67]	7	2	1
Spain [34,38,56,60,68,89,92]	7	4	2
Taiwan [10,37,62,69,80,82,94]	7	5	2
China [58,71,72,75,85]	5	4	
Israel [21,45,90,91]	4	3	
Germany [9,39,41,61]	4	3	
Italy [23,31,35]	3	3	
Japan [74,79,84]	3	3	
Tanzania [17,64,73]	3	3	
India [47,48,78]	3	1	1
Canada [63,65,83]	3	2	
UK [20,28,87]	3	3	
France [66,77]	2	1	1
South Africa [13,81]	2	1	
Brazil [13,81]	2	2	
Greece [88]	1	1	
Hungary [93]	1	1	
Lebanon [25]	1	-	
Malaysia [27]	1	-	1
Mexico [70]	1	1	
Saudi Arabia [18]	1	1	
Turkey [76]	1	1	
Continent			
Asia [10-12,14,15,18,21,22,23,25,27,29,33,36,37,40,42-45,47-53,55,57,58,62,69,71,72,74,74,78-80,82,84-86,90,91,94]	46	29	6
Europe [9,20,23,28,31,34,35,38,39,41,56,60,61,66,68,76,77,87-89,92,93]	22	17	3
North America [8,16,26,30,46,59,63,65,67,83]	10	4	1
Africa [13,17,64,73,81]	5	4	-
South America [19,32,70]	3	3	-
More than 1 continent [54]	1	-	-

Income group			
High-income countries [8-12,14-16,18,20,21,23,26,28-31,34-42,44-46,49,50,55-57,59-63,65-69,74,77,79,80,82-84,87-94,]	60	41	8
Low- and middle-income countries [13,17,19,22,24,25,27,32,43,48,51-53,58,64,70-73,75,76,78,81,85,86]	26	16	2
High-income countries AND Low- and middle-income countries [54]	1	-	-
Study design			
Case cohort study [8,10,22-26,29,38,42,44,53,56,59,61-63,65-67,83-85]	24	14	
Retrospective cohort study [9,11-15,18,19,21,27,31-36,39-41,43,45,46,48-52,57,58,69,71,72,74-76,79-82,86,87,91,93,94]	44	32	
Prospective cohort study [16,17,28,30,37,47,54,60,64,68,70,73,77,78,88-90,92]	18	11	
Year group			
1991-1999 [8,58,13,14,15,60,19,23,26,34,44,91,92]	13	10	-
2000-2009 [9-12,16-18,20-22,24,25,27-33,35-43,45,47-50,52,53,55,56,59,61,62,65-67,87-90,93,94]	49	31	6
2010-2018 [46,51,52,57,63,64,68-86]	25	16	4
Pathogen			
Escherichia coli [9,22,28,31,33-35,38,41,43,50,53,56,57,66,68,69,71,74,84,85,89,92]	23	16	3
Klebsiella pneumoniae [13,14,18,19,23,27,30,32,39,41,45,59,60,72,76,81,93,94]	17	11	1
E. coli and *K. pneumoniae* [8,11,12,15,24,26,36,41,42,44,46,48,49,52,55,58,61,67,83,86,87]	20	13	2
Gram-negative bacteria [10,16,17,20,21,25,29,37,40,47,51,54,62-65,70,73,75,77-80,82,88,90,91]	27	17	4
Study setting			
Entire hospital [8,9,14,16,18-25,27,28,31-36,38-44,46-48,50-53,56-58,60,63-67,71,72,74,80,83,84,88-94]	57	40	7
Intensive care unit [30,59,62,73,77-79,86,87]	9	5	1
Pediatric ward [15,17,26,49,55,76,81,86]	8	7	-
Neonatal ward [13,59,62,69,73]	5	3	-
Neonatal intensive care unit [59,62,73]	3	2	-
Medical ward [11,37,68]	3	-	2
Not provided [29,45]	2	-	-
Emergency Department [10,82]	2	2	-
Surgical ward [30,54]	2	-	-
Burn unit [30]	1	-	-
Oncology [70]	1	1	-
Referral centre for hepatopacreaticobiliary diseases [75]	1	-	-
Hematological [12]	1	1	-

Study population			
All kinds of patients [8-11,12,16,18-25,27,28,32,33,37-39,41-44,46-48,50-54,56,58,60,61,63-67,74,80,82-84,88,90-93]	55	36	7
Intensive care unit patients [30,77-79,85,87]	6	3	1
Children [15,17,26,49,55,76,81,86]	8	7	-
Neonates [13,59,62,69,73]	5	3	-
Cancer patients [31,49,57,70,89]	5	5	-
Immunocompromised patients [49]	1	1	-
Diabetic patients [94]	1	1	-
Elderly patients [68]	1	-	1
Patients with chemotherapy/stem cell transplantation [12,89]	2	2	-
Patients after prostatitis biopsy [40]	1	-	1
Lungs transplantation patients [45]	1	-	-
Hematological patients [71]	1	1	-
All except cardiothoracic therapy, transplant surgery, burns [72]	1	1	
Patients with pyogenic liver abscess [75]	1	-	-
Data reported			
Treatment information [8,10-11,21-24,28-36,38,42-47,49,50,52-63,65,66,68-94]	74	50	6
Appropriateness of treatment [8,10-12,14,15,17-19,21-24,28-36,38,42-44,46,47,49,50,52-54,56-58,60-63,65,66,68,70-72,74,75,77,79,81-84,87-94]	62	45	5
Empirical therapy [12,14,15,22,23,31,33-36,38,42,49,50,54,56,57,61,74,79,81,92]	22	16	2
Treatment outcome [8,10-19,23,24,28-36,38,42-47,49,50,52-55,57-63,65,66,70-72,74,76-79,81-84,86-90,92-94]	64	45	3
Minimum inhibitory concentration results [8,9,11,12,14-17,20-23,25,26,30,31,33-39,41,42,45,48-50,52-57,60,61,64,66,67,74-76,78,79,81,83-85,87,92,93]	52	34	4
AmpC genotyping [8,9,15,30,39,44,48,54,55,63,64,68,84]	13	6	2

Supplementary table S4: Characteristics for each study

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Lautenbach E[8]	1997-1998	USA	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality; LOS	Risk factors for infection with ESBL-producing pathogens, difference in clinical outcomes of infections: resistant vs. susceptible organisms	EC, KP
Kim SH[12]	2007-2008	South Korea	Cohort study, Retrospective	Non-ESBL-infection	Patients who received either chemotherapy or stem cell transplantation; neutropenic fever	Hematological ward, Others	All-cause mortality (28 day)	Risk factors for acquisition of ESBL, appropriateness of empirical antimicrobial therapy, clinical outcomes in relation to ESBL production	EC, KP
Chayakulkeere M[51]	2015-2015	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Prevalence & risk factors for infections with & antibiotic susceptibility patterns of & outcomes of patients infected with ESBL-producing-GNB	GNB
Apisarnthanarak A[52]	2003-2007	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Predictors for mortality associated with community-onset BSI with ESBL-producing pathogens, initial empirical antimicrobial regimens, associated hospital resource utilisation,costs accrued after diagnosis of BSI	EC, KP
Apisarnthanarak A[53]	2003-2004	Thailand	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Mortality associated with community-onset infection due to ESBL-producing pathogens, associated hospital resource use, post-infection hospital cost	EC
Jean SS[54]	2010-2011	Portugal, Columbia, the Philippines, Taiwan, Thailand	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Surgical ward	Attributable mortality, LOS	Clinical impact on hospitalised patients with community-acquired complicated intra-abdominal infection: ESBL-producing- vs. non-ESBL-producing pathogens	GNB
Lee J[55]	1999-2005	South Korea	interventional studies	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	impact of a change in antibiotic policy on ESBL-prevalence	EC, KP
Briongos-Figuero L.S[56]	2009-2010	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Characteristics &associated risk factors for EBSL-enterobacteria-UTIs	EC
Ha YE[57]	2010-2012	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with cancer	Entire hospital	All-cause mortality (28 day)	Clinical &molecular epidemiology of ESBL-EC bacteraemia, clinical impact of ESBLs on patient outcome	EC
Du B[58]	1997-1999	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for nosocomial ESBL-EC- and ESBL-KP- bacteraemia & influence on patient outcome.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Stone PW[59]	2001	USA	Case cohort study	Non-ESBL-infection	Neonates at NICU	NICU	LOS	costs of interventions aimed at controlling the outbreak, attributable length of stay associated with infection and colonisation with ESBL-KP	KP
Pillay T[13]	1995-1996	South Africa	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Use of piperacillin/tazobactam in treatment of KP- infection	KP
Kim BN[14]	1999-2000	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, LOS	Prevalence & clinical characteristics of ESBL-KP- bacteraemia, impact of ESBL- production on outcome of patients with KP-bacteraemia in endemic situation.	KP
Kim YK[15]	1993-1998	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Risk factors & clinical outcomes & clinical responses to treatment of ESBL-EC- and ESBL-KP-bacteraemia, prevalence and types of their ESBLs	EC, KP
Bhavnani SM[16]	2001-2002	USA	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Risk factors for occurrence of invasive ESBL-EC- and ESBL-KP-infections, factors associated with clinical outcome, drug regimens for treatment of infections associated ESBL/non-ESBL strains in real-life clinical practice, clinical response rates for patients treated with cephalosporins/other classes of antimicrobial agents, /carbapenems, clinical response for those patients with infection associated with ESBL and non–ESBL-producing strains with MIC values V8 Ag/mL treated with cephalosporins.	GNB
Blomberg B[17]	2001-2002	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates, children	Pediatric ward	All-cause mortality	Prevalence & clinical implications of ESBL production in EC-,KP-, Salmonellae- septicemia	GNB
Pena C[60]	1993-1995	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Clinical epidemiology& outcome of ESBL-KP- bacteraemia, relevance of ESBL strains in mortality of patients with hospital-acquired KP-BSI.	KP
Kola A[61]	2002-2004	Germany	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Outcomes of ESBL-EC- and ESBL-KP-infections	EC, KP
Tsai MH[62]	2001-2012	Taiwan	Case cohort study	Control group: non-ESBL-infection, second control group: all hospitalised patients	Neonates at NICU	NICU	Attributable mortality, all-cause mortality, LOS	Clinical features& risk factors& molecular epidemiology of ESBL-GNB	GNB
Maslikowska JA[63]	2010-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	Differences in clinical & microbiological outcome, mortality, and/or hospital resource use: ESBL-EC- and ESBL-Ks- vs non-ESBL-EC- and non-ESBL-Ks-infections	GNB

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Onken A[64]	2012-2013	Tanzania	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Most common bacterial pathogens causing BSI, antimicrobial susceptibility	GNB
Nguyen ML[65]	2005-2010	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Risk factors for & patient outcomes associated with ESBL-EC- and ESBL-Ks- bacteraemia, appropriateness of empiric antibiotic therapy & effect of inappropriate empiric therapy on outcomes	GNB
Denis B[66]	2005-2009	France	Case-control study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Prevalence & risk factors for ESBL-EC bacteraemia, impact on length of stay &30day mortality	EC
Chopra T[67]	2004-2009	USA	Case cohort study	Case 2(Control1): non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Predictors of ESBL-EC- and ESBL-KP-BSI, focus on cefepime exposure.	EC, KP
Panhotra BR[18]	2001-2003	Kingdom of Saudi Arabia	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors & clinical outcome of ESBL-KP-bacteraemia (hospital acquired)	KP
Marra AR[19]	1996-2001	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	ESBL-KP- associated mortality	KP
Skippen I[20]	2003-2005	UK	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-invasive transmission of organism in the healthcare setting	GNB
Schwaber MJ[21]	2000-2003	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Outcomes of ESBL-production in Enterobacteriaceae-bacteraemia.	GNB
Apisarnthanarak A[22]	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All adult patients	Entire hospital	All-cause mortality, LOS	Clinical & molecular epidemiologic factors associated with community onset ESBL-EC- infections, hospital resource utilisation, estimate costs associated with medical care (hospitalised patients)	EC
Tumbarello M[23]	1999-2003	Italy	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS, ICU-LOS	Factors associated with isolation of ESBL- KP-strains	KP
Zeistner R[9]	2008-2010	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital,	All-cause mortality, LOS	Difference in mortality: ESBL-EC-BSIs vs. non-ESBL-EC-BSIs, molecular epidemiology of ESBL-positive isolates	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Apisarnthanarak A[24]	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-infections (healthcare associated)	EC, KP
Kanafani ZA[25]	2003	Lebanon	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Epidemiology of infections with ESBL-EC and ESBL-Ks at AUBMC risk factors & outcomes of infections - focus on effect of prior antibiotic administration & the risks imparted by specific classes of antimicrobial agents	GNB
Zaoutis TE[26]	1999-2003	USA	Case cohort study	Non-ESBL-infection	Children	Entire hospital	All-cause mortality, LOS	Risk factors & outcomes associated with ESBL-EC-and ESBL-KP-BSI	EC, KP
Loh LC[27]	2003-2004	Malaysia	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Impact of ESBL-KP-respiratory tract infections on hospital mortality, requirement for mechanical ventilation & length stay	KP
Melzer M[28]	2003-2005	UK	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Differences in mortality & length of hospital stay &time from bacteraemia to death in patients with ESBL-EC- vs. non-ESBL-EC-bacteremic-infection	EC
Song KH[29]	2000-2006	South Korea	Case cohort study	Non-ESBL-infection	Patients with spontaneous bacterial peritonitis	Not provided	All-cause mortality (28 day)	Outcomes of ESBL-EC-and ESBL-Ks- vs non-ESBL-EC-and ESBL-Ks-SBP (based on isolation from ascites), impact of ineffective initial antimicrobial therapy on outcome in patients with ESBL-EC- and ESBL-Ks-SBP, risk factors for infection by ESBL-producing microorganisms.	GNB
Bennett JW[30]	2004-2008	USA	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU, Surgical ward, Burn unit	All-cause mortality (28 day)	ESBL types and strain variability, presence of host factors to determine potential role in morbidity and mortality during ESBL-KP-infections	KP
Trecarichi EM[31]	2000-2007	Italy	Cohort study, retrospective	Non-ESBL-infection	Patients with hematological malignancies	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality in patients suffering from hematological malignancies with concurrent EC-bacteraemia. Focus on impact of ESBL- production & fluoroquinolone resistance by bacterial isolates	EC
Tuon FF[32]	2006-2009	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Risk factors & mortality rate in ESBL-KP-bacteraemia	KP
Kang CI[33]	2008-2009	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors of ESBL-EC among community-onset bacteraemia, treatment outcomes	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Pena C[34]	1996-2003	Spain	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality among patients with EC- infections	EC
Tumbarello M[35]	2006	Italy	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	ICU, Medical ward, Entire hospital, surgical wide	All-cause mortality (21 day), LOS	Clinical &economic impacts of ESBL production, inadequate Initial Antibiotic Therapy of EC-BSI	EC
Kang CI[36]	2006-2009	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality (28 day)	Impact of ESBL-producing bacteraemia on outcome in patients with hematologic malignancy.	EC, KP
Wu YH[37]	2009-2012	Taiwan	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Medical ward	LOS	Host-related risk factors for community-onset UTI due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production, clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens	GNB
Rodriguez-Bano J[38]	2004-2006	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Epidemiology& risk factors (focus on previous antimicrobial use) & mortality rate for patients with ESBL-EC-COBSI	EC
Gürtnke S[39]	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Distribution of ESBL genotypes, hospital mortality in cases of ESBL-KP-BSI	KP
Oh MM[40]	2006-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients after Prostatitis Biopsy	Entire hospital	LOS	Impact of ESBL-positive-strains on clinical course & progression to chronic prostatitis in patients with postbiopsy acute prostatitis.	GNB
Leistner R[41]	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Financial disease burden attributable to ESBL-positive species in cases of EC-and KP-BSI	EC, KP
Lin JN[10]	2005-2009	Taiwan	Case cohort study	Non-ESBL-infection	All kinds of patients	Emergency Room	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Clinical & microbiological characteristics, risk factors for acquisition of infection, prescription of initial empirical antibiotics mortality rate of infection	GNB
Ku NS[42]	2006-2010	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Clinical usefulness of breakpoints for treatment of Enterobacteriaceae-bacteraemia, (focus on EC- and Ks-bacteraemia): CLSI 2009- vs. CLSI 2010-guidelines.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Anunnatsiri S[43]	2005-2006	Thailand	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Incidence of ESBL-EC-septicemia, factors associated with infection & clinical outcomes	EC
Kang CI[44]	1998-2002	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Hospital-wide	All-cause mortality (28 day)	Risk factors for mortality & treatment outcome of ESBL-EC- and ESBL-KP-BSI	EC, KP
Raviv Y[45]	2004-2007	Israel	Cohort study, retrospective	Control group: non-ESBL-infection, second control group: no infection	patients with lung transplantation	Not provided	All-cause mortality (28 day)	Outcomes of lung transplant recipients infected by CRKP and ESBL carbapenem-sensitive KP (referred to MDR-KP)	KP
Kim HJ[11]	2005-2010	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Medical ward	All-cause mortality (28 day), LOS	Clinical outcome of patients with biliary tract infection: ESBL-producing bacterial isolates vs. non-ESBL-producing-bacterial isolates, predictors of poor prognosis, impact of ineffective antimicrobial therapy on clinical outcome	EC, KP
MacVane SH[46]	2011-2012	USA	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	clinical & economic outcomes of patients with ESBL-EC- and ESBL-KP-UTI vs. non-ESBL-EC- and non-ESBL-KP-UTI	EC, KP
Abhilash KP[47]	2007	India	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Prevalence & risk factors & outcome of antibiotic treatment among hospitalised patients with ESBL-EC- and ESBL-Ks-BSI	GNB
Shanthi M[48]	2006	India	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Prevalence & impact on clinical outcome of ESBL-production among nosocomial isolates of EC & KP	EC, KP
Han SB [49]	2009-2013	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children (immunocompromised, with cancer, neutropenic fever)	Pediatric ward	Attributable mortality, all-cause mortality (28 day)	Clinical outcomes of ESBL-EC- and ESBL-KP-bacteraemia & their antibiotic susceptibilities	EC, KP
Lee S[50]	2009-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with Acute Pyelonephritis	Entire hospital	All-cause mortality (14 day), LOS	Impact of ESBL on clinical outcomes of Acute Pyelonephritis treated with empirical ceftriaxone (which was inappropriate for ESBL-producing organisms)	EC
Artero A[68]	2013-2015	Spain	Cohort study, prospective	Non-ESBL-infection	Elderly	Medical ward	All-cause mortality, LOS	Identify clinical factors to predict ESBL-EC among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-EC	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Chen IL [69]	2004-2015	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Compare the clinical characteristics & laboratory data of preterm babies with EC BSI: survival vs. nonsurvival groups, ESBL vs non-ESBL groups, determine the predictive factors of EC BSI in preterm babies	EC
Islas-Munoz B[70]	2016-2017	Mexico	Cohort study, prospective	Non-ESBL-infection	Cancer patients	Oncological ward	All-cause mortality (28 day)	Evaluate the clinical epidemiological characteristics & risk factors associated with mortality in cancer patients with BSI-special emphasis on MDR bacteria	GNB (and others)
Ma J[71]	2012-2015		Cohort study, retrospective	Non-ESBL-infection	Patients with hematological diseases	Entire hospital	All-cause mortality (28 day)	Evaluate the antimicrobial resistance & clinical features & risk factors for septic shock & death of nosocomial EC-BSI	EC
Man MY[72]	2009-2016	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients, except patients from Burn unit, transplant surgery ward or with thoracic therapy	Entire hospital	All-cause mortality (28 day)	Evaluate the incidence & clinical characteristics & outcomes of patients with KP BSI in critical care & general ward settings	KP
Marando R[73]	2016	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates	NICU	All-cause mortality	Investigate factors associated with ESBL-PE neonatal sepsis & mortality among neonates, characterise selected isolates to show virulence potential & transmission dynamics	GNB
Namikawa H[74]	2011-2015	Japan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate clinical characteristics of patients with ESBL-EC-BSI	EC
Shi SH[75]	2008-2015	China	Cohort study, retrospective	Non-ESBL-infection	Patients with pyogenic liver abscess	Centre for hepatopancreaticobiliary diseases	All-cause mortality, LOS	Aetiology & morbidity & clinical characteristics of pyogenic liver abscess caused by ESBL-PE	GN
Tanir Basaranoglu S[76]	2011-2015	Turkey	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	Assess risk factors for health care associated ESBL-KP-BSI in children, analyze clinical outcomes: ESBL-KP vs. non-ESBL-KP	KP
Razazi K[77]	2009-2015	France	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality, LOS, ICU-LOS	Determine, among ESBL-PE carriers, the prevalence & associated factors & clinical impact of ESBL-PE pneumonia, determine factors associated with ICUAP caused by carbapenem-resistant bacteria	GNB

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Ray S[78]	2014-2016	India	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Investigate spectrum of microbial resistance pattern in the community and their effects on mortality	GNB
Haruki Y[79]	2006-2016	Japan	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Compare the clinical characteristics & outcomes of critically ill patients in an ICU, who were hospitalised for BSI caused by ESBL-EC or non-ESBL-EC.	GNB
Lin WT[80]	2009-2014	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate the clinical manifestations & bacteriological features of culture-proven, GNB arthritis	GNB
Buys H[81]	2006-2011	South Africa	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Describe the clinical presentation of KPBSI, risk factors associated with ESBL-KPBSI, antibiotic susceptibility patterns of the KP isolates & KPBSI mortality including factors associated with in-patient mortality	KP
Lee CC[82]	2008-2013	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Emergency Department	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Analyse the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics & bacteraemia severity by using a propensity-matched analysis (PSM)	GNB
Huang YY[83]	2011-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Determine cumulative incidence of ESBL urosepsis, identify major risk factors for ESBL urosepsis, determine impact of international travel on development of ESBL urosepsis	EC, KP
Komatsu Y[84]	2008-2013	Japan	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Identify risk factors & clinical outcomes in patients with BSI due to ESBL- or carbapenemase-producing EC, determine prevalence & genetic background	EC
Liu MM [85]	2011-2016	China	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	ICU-patients	ICU	All-cause mortality	Identify risk factors for ESBL-producing ECBSI among carriers at ICU	EC
Nivesvivat T[86]	2010-2017	Thailand	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality, LOS	Determine prevalence, risk factors & clinical outcomes of ESBL-producing EB in paediatric BSI	EC, KP

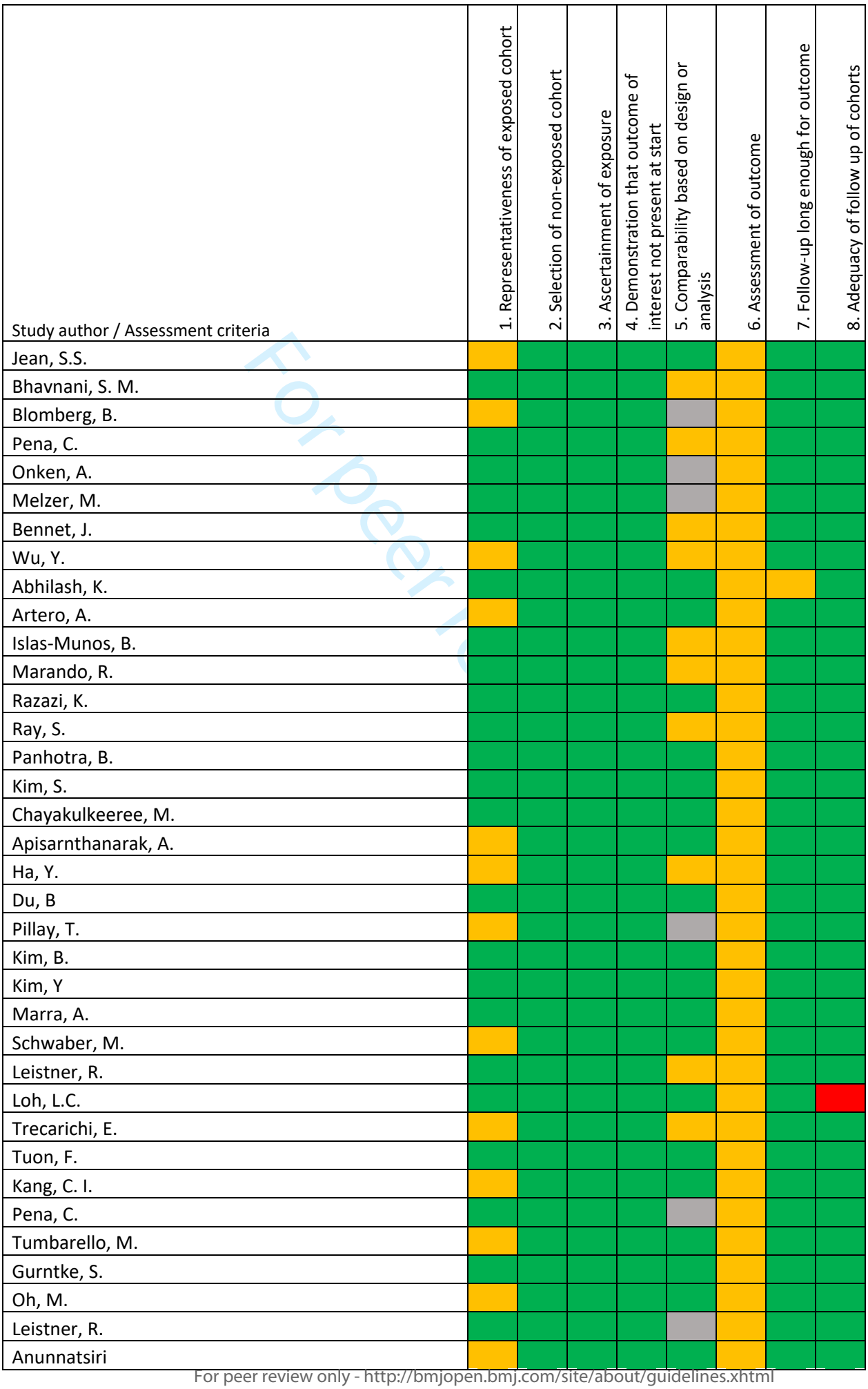
	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Cordery RJ[87]	2004-2006	UK	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Elucidate specific risk factors for the acquisition of ESBL infection in the ICU; all-cause mortality (in ICU) compared in patients with infections due to ESBL- and non-ESBL-producing organisms	GNB
Paikos GL[88]	2003-2005	Greece	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Identify risk factors associated BSI caused by integron-carrying EB; evaluate the consequences of these genetic elements on patient outcome	GNB
Gudiol C[89]	2006-2008	Spain	Cohort study, prospective	Non-ESBL-infection	Cancer patients and hematopoietic stem cell transplant patients	Entire hospital	All-cause mortality	Assess clinical features, risk factors, molecular epidemiology & outcome of ESBLEC BSI in hospitalised cancer patients	EC
Marchaim D[90]	2006-2008	Israel	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Define predictors & outcomes of ESBL BSI among patients with bacteraemia due to EB upon hospital admission	GNB
Menashe G[91]	1997	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Determine: prevalence of ESBL-P organisms among adult patients with nosocomial EB BSI treated in our institution; association between ESBL production & resistance to other antibiotics; clinical characteristics of patients with nosocomial ESBL-P BSI compared with those infected with non-producing strains; impact of ESBL production on outcome of patients with nosocomial EB BSI	GNB
Ortega M[92]	1991-2007	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Describe source, resistance rate to fluoroquinolone & beta-lactam antibiotics and mortality of EC BSI episodes in a single institution; identify predictive factors for isolation of fluoroquinolone-resistant or ESBL- producing strains.	EC
Sziglyi M[93]	2005-2008	Hungary	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality,	Investigate risk factors for & outcomes of BSI caused by ESBL-producing and ESBL-non-producing KP	KP
Tsai SS[94]	2005-2006	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Diabetic patients	Entire hospital	All-cause mortality	Analyze characteristics, risk factors & outcomes of diabetic patients with community- vs. hospital-acquired KP BSI	KP

EC = *Escherichia coli*
KP = *Klebsiella pneumoniae*
GNB = Gram-negative bacteria
BSI = Bloodstream infection
UTI = Urinary tract infection
ICU = Intensive care unit
NICU = Neonatal intensive care unit
ESBL-PE = Extended-spectrum beta-lactamase-producing Enterobacteriaceae
EB = Enterobacteriaceae
LOS = Length of stay

Supplementary table S5: Risk of bias assessment of case cohort studies according to Newcastle - Ottawa quality assessment scale:

Assessment criteria / Study author	1. Is the case definition adequate?	2. Representativeness of the cases:	3. Selection of Controls	4. Definition of Controls	5. Comparability of cases and controls on the basis of the design or analysis	6. Ascertainment of exposure	7. Same method of ascertainment for cases and controls	8. Non-Response rate
Lautenbach, E.								
Apisarnthanarak, A.								
Briongos-Figuero, L-S.								
Stone, P.W.								
Kola, A.								
Tsai, M.H.								
Maslikowska, J.A.								
Nguyen, M. L.								
Denis, B.								
Chopra, T.								
Skippen, I.								
Apisarnthanarak, A.								
Tumbarello, M.								
Apisarnthanarak, A.								
Kanafani, Z. A.								
Zaoutis, T. E.								
Song, K. H.								
Kang, C. I.								
Rodriguez-Bano, J.								
Lin, J. N.								
Ku, N. S.								
Kang, C. I.								
Huang, Y. Y.								
Komatsu, Y.								
Liu, M. M.								

Risk of bias assessment of cohort studies according to Newcastle - Ottawa quality assessment scale:



Raviv, Y.								
Kim, H.J.								
MacVane, S.								
Shanthi								
Han, S.B.								
Lee, S.								
Chen, I-L.								
Ma, J.								
Man, M.								
Namikawa, H.								
Shi, S.								
Tanir Basarangolu, S.								
Haruki, Y.								
Lin, W.								
Buys, H.								
Lee, C.C.								
Nivesvivat, T.								

Supplementary table S6: Source of heterogeneity among effect estimates in studies on ESBL bloodstream infections in comparison with patients with non-ESBL bloodstream infections assessed using univariate meta-regression:

Subgroups / Outcome	All-cause mortality	Length of Stay
Mortality time	0.85	-
Pathogen	0.45	0.34
Study design	0.51	0.21
Study country	0.22	0.09
Income classification	0.17	0.80
Study period	0.57	0.78
Study setting: ICU ward	0.78	0.97
Study setting: Neonatal ward	0.62	0.97
Study setting: Pediatric ward	0.96	0.96
Study population: ICU patients	1.00	-
Study population: Children	0.96	0.96
Study population: Neonates	0.62	0.97
Information about therapy	0.53	
Appropriatness of therapy reported	0.68	
Information about outcome of therapy	0.74	-
MIC reported	0.28	-

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	suppl.material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 and suppl. material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	suppl.material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 and suppl. material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030266.R2
Article Type:	Original research
Date Submitted by the Author:	13-Nov-2019
Complete List of Authors:	Shamsrizi, Parichehr; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Gladstone, Beryl Primrose ; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Carrara, Elena; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Luise, Dora; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Cona, Andrea; ASST Santi Paolo e Carlo, Clinic of Infectious and Tropical Diseases, Department of Health Sciences Bovo, Chiara; Integrated University Hospital of Verona, Medical Direction Tacconelli, Evelina; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Epidemiology
Keywords:	Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

AUTHORS:

Parichehr Shamsrizi[1], Beryl Primrose Gladstone[1], Elena Carrara[2], Dora Luise[2], Andrea Cona[3], Chiara Bovo[4], Evelina Tacconelli[1,2]

AFFILIATIONS:

1) Division of Infectious Disease, Department of Internal Medicine I, DZIF Partner site, Tübingen University Hospital, Tübingen, Germany
2) Division of Infectious Disease, Department of Diagnostic and Public Health, University Hospital of Verona, Verona, Italy
3) Clinic of Infectious and Tropical Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
4) Medical Direction, University Hospital of Verona, Verona, Italy

CORRESPONDING AUTHOR: Elena Carrara, MD

Address: Division of Infectious Disease, Department of Diagnostic and Public Health, University Hospital of Verona, Verona, Italy

Piazzale L.A. Scuro 10, Dipartimento di Malattie Infettive, Policlinico Borgo Roma, 37100 Verona, Italy.

Phone number: +39 3339566252

Email: elena.carrara@univr.it

WORD COUNT: 2827

ABSTRACT

Objective To assess the variation of effect estimates in the analysis of mortality and length of stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*.

Design Systematic review and meta-analysis

Methods Literature search for clinical studies from 1 January 1960 to 1 October 2018 was conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream infections (BSIs) and non-invasive infections. Any change in the effect estimates was assessed by grouping studies according to design, setting, economy-based country classification, reporting period, microbiological aetiology, infection type, and adjustment for appropriateness of empirical treatment. The impact of ESBL production was calculated using random effect meta-analysis and heterogeneity was evaluated by I^2 statistics and metaregression.

Results Eighty-four studies including 22,030 patients and 149 outcome measures were included in the meta-analysis. Most studies were retrospective cohorts from high-income countries, providing unadjusted estimates. ESBL production in patients with BSIs (56 studies) increased the RR for all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; p<0.001), attributable mortality (16 studies) by 1.75 (95% CI: 1.448-2.108; p<0.001), and WMD in the intensive care unit by 3.07 days (95% CI: 1.61-4.54; p<0.001). WMD in hospital LOS was significantly higher in BSIs (4.41 days; 95% CI: 3.37-5.46; p<0.001) and non-invasive (2.19 days; 95% CI: 1.56-2.81; p<0.001). Subgroup analyses showed variation of estimates by study design, population, strain, and assessment of appropriateness of empiric treatment. High heterogeneity was observed in all analyses.

Conclusions Current evidence of the clinical burden of infections caused by ESBL-producing bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from retrospective studies. Despite these limitations, ESBL production in strains causing BSIs seems associated with higher all-cause and attributable mortality and longer hospitalisation.

KEYWORDS

Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Evidence of the impact of ESBL production on mortality and length of stay in strains causing bacteremic and non-bacteremic infections was collected systematically.
- Effect of multiple epidemiological and clinical variables was assessed in the calculation of estimates.
- Heterogeneity among studies was assessed.
- Only few studies had been performed in high-risk populations or low-income countries.

INTRODUCTION

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* are responsible for high morbidity and mortality worldwide.[1,2,3] The 2018 World Health Organization list of antibiotic-resistant pathogens identified mortality as the most important criteria to prioritise bacteria for research and development of new, effective antibiotics.[1] In this prioritisation exercise, ESBL-producing *Enterobacteriaceae* were designated a critical priority because of their high all-cause mortality and high prevalence globally in healthcare-associated and community-acquired infections. The incidence and attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing *Enterobacteriaceae*, in European countries has been recently estimated using a modelling analysis.[4] In 2015 ESBL-producing *Escherichia coli* was responsible for almost 300,000 infections in Europe and 9,000 attributable deaths, and ESBL-producing *Klebsiella pneumoniae* caused around 70,000 infections and more than 3,500 deaths. The major limitation of this analysis is the sparseness of evidence on mortality due to ESBL-producing bacteria, which was limited largely to studies conducted in high-income countries.

Two systematic reviews have been performed to define the impact of ESBL production on mortality due to *Enterobacteriaceae*.[2,3] Both meta-analyses included studies targeting bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated bacteraemia compared to non-ESBL *Enterobacteriaceae* bacteraemia. A major drawback of the analyses, highlighted by the authors, was the lack of control for confounding and limited adjustment for empiric therapy. No systematic review has been performed to assess attributable mortality and other indicators of clinical impact such as length of stay (LOS).

Because estimates of clinical burden drive policy design for antibiotic stewardship and infection control interventions, precise and current estimates are essential. The objective of this systematic review and meta-analysis was to assess the variation of effect estimates in the analysis of mortality and LOS in patients with infections due to ESBL-producing *Enterobacteriaceae*.

METHODS

Literature search strategy

The search was performed by 2 researchers (BPG and PS) in PubMed on 05 October 2018 using search terms (supplementary table S1) relevant to the following combinations: (ESBL AND Escherichia coli AND mortality) OR (ESBL AND Klebsiella pneumoniae AND

mortality) OR (ESBL AND Escherichia coli AND length of stay OR length of hospitalisation) OR (ESBL AND Klebsiella pneumoniae AND length of stay OR length of hospitalisation). Reference lists of retrieved articles were also searched.

Eligibility criteria

We included all clinical studies with a comparison group assessing all-cause mortality, attributable mortality, and overall LOS and intensive care unit stay (ICU) LOS in hospitalised patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018 irrespective of the clinical setting and study design were included. No language restriction has been applied. Diagnostic studies, reviews, case reports, non-clinical studies, and abstracts of conference presentations were not included.

Data extraction

Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted data. In case of disagreement, a third reviewer (DL) was consulted. Extracted data were collected in an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of publication, year of study, time of data collection, study design, comparison group, study setting, population, aetiology, type and site of infection, and raw data related to mortality and LOS/ICU-LOS. Countries were classified as high-, middle-, or low-income using the World Bank Atlas method.[5] Adjusted effect estimates such as odds ratios (ORs) or hazard ratios and quality indicators such as reporting of antibiotic therapy, appropriateness of empirical treatment, resistance mechanisms, and minimum inhibitory concentrations (MICs) were also extracted.

Mortality data were extracted as all-cause mortality or attributable mortality as defined in the studies. Where available, prespecified time periods for mortality assessment (i.e., 14 days, 28 days, in-hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean and standard deviation or median and interquartile range.

Data analysis

The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in patients with ESBL infections compared with those in patients with non-ESBL infections and, where available, with uninfected patients. The impact of ESBL production on attributable and all-cause mortality was calculated with random effect meta-analysis and expressed as RR with

95% confidence interval (CI). WMD in days with 95% CI was calculated to express the excess in LOS and ICU-LOS.

Variation of the effect estimate was assessed by grouping the studies according to the following study/outcome characteristics: mortality time assessment (7 vs 14 days), aetiology (*E. coli* vs *K. pneumoniae*), infection localisation, clinical setting (paediatric, oncology, ICU), economic country areas (high-income countries [HICs] vs low- and medium-income countries [LMICs]), study design, assessment of empiric therapy, and year. Studies were classified according to the type of infections evaluated. Studies on BSIs were defined as those in which patients had positive blood cultures and were admitted to the hospitals with signs and symptoms of systemic inflammatory response and requiring therapy, similarly to the definition adopted by the most recent cohort studies on ESBL infections.[6] Non-invasive infections included non-bacteremic patients with only localised signs and symptoms of infection (such as urinary tract infections or superficial surgical site infections).

Subgroup analysis was computed only if more than 2 studies were available for each group. Heterogeneity was evaluated by using I^2 statistics and metaregression. Overall significance testing was carried out using Wald tests adjusted using the Bonferroni correction. The unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment. Reporting and publication bias was presented in funnel plots (supplementary figure 1 and 2) and tested by Egger's test. Statistical analyses were performed using Stata version 15. Risk of bias was assessed independently by two authors (PS, DL) using the Newcastle - Ottawa quality assessment scale for cohort studies.[7] Studies were classified as low, moderate, or high quality according to AHRQ standards (supplementary table S2). All meta-analyses were performed in accordance with the Cochrane Collaboration recommendations[8] and reported according to the PRISMA statement.[9]

The protocol is available online.

(https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf)

Patient and Public Involvement

There was no patient or public involvement in this systematic review of published literature.

RESULTS

Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an

evidence base of 87 studies (Figure 1).[10-96] The 87 studies included in the qualitative analysis were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies), Thailand (7), USA (7), Taiwan (7), and Spain (7). Sixty (68.9%) studies were performed in HICs, 26 (29.9%) in LMICs, and 1 included both HICs and LMICs.[56] About half (44, 50.6%) were retrospective cohort studies, 24 (27.6%) case cohort studies, and 18 (20.7%) prospective cohort studies; 1 study had an interventional design.[57] The comparison group was patients with infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-infected patients in 2 (2.3%), and both control groups in 3 (3.5%). Most (57, 65.5%) studies included data from the entire hospital, while a few focused on specific settings, mainly ICUs (9, 10.3%) and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were *E. coli* (23, 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is provided in online supplementary table S3.

Because data in 3 studies [22,61,87] were insufficient for quantitative analysis, 84 (96.6%) studies were included in the meta-analysis analysing data from 22,030 patients and 149 outcome measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study characteristics for all studies are provided in online supplementary table S4. 49 (58.3%) studies were of high quality, 23 (27.3%) were of moderate quality, and 12 (14.3%) were of low quality (supplementary table S5).

All-cause mortality

All-cause mortality was reported in 81 studies including 21,942 patients (56 on BSIs and 7 on non-invasive infections). ESBL production in patients with BSIs increased all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; p<0.001; I^2=45.3%; p<0.001) while studies including non-invasive reported a RR of 1.58 (95% CI: 1.23-2.02; p<0.001) (supplementary figure 3). Among the BSI patients, the RR increased over time from 1.56 (95% CI: 1.15-2.11; p=0.004) in 1991-1999 to 1.74 (95% CI: 1.50-2.01; p<0.001) in 2000-2009, and it was stable in 2010-2018 (1.72, 95% CI: 1.39-2.13; p<0.001). The RR was higher in studies assessing appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; p<0.001) than in those that did not (RR=1.55; 95% CI 1.26-1.90; p<0.001). The subgroup analysis by pathogen showed that ESBL production increased the RR in BSIs due to *E. coli* (RR=1.82; 95% CI: 1.50-2.21; p<0.001) compared to those due to *K. pneumoniae* (RR=1.48; 95% CI: 1.17-1.87; p=0.001). Stratification by population age showed a higher RR in paediatric population (RR=2.09; 95% CI: 1.62-2.71; p<0.001). Effect estimates did not vary significantly by study country, mortality time assessment (14 vs 28 days), ESBL molecular resistance mechanisms, or study

design (Figure 2 and online supplementary figure 4). Adjusted estimates for inappropriate empirical antibiotic therapy were provided for 14 studies. The pooled unadjusted OR for all-cause mortality was 2.91 (95% CI: 2.23-3.81; p<0.001, I^2=27.1%; p=0.164) and the pooled OR after adjusting for receipt of appropriate empirical treatment was 3.22 (95% CI: 1.53-6.76; p=0.002; I^2=87.5%; p<0.001). The impact of ESBL production on LOS and mortality varied according to the infection type, with higher effect in intra-abdominal, respiratory and BSIs (supplemental figure 5 and 6).

Attributable mortality

Attributable mortality was analysed in 16 studies including 2,885 patients. All studies were performed in HICs. ESBL production in patients with BSIs increased the risk of attributable mortality by a factor of 1.75 (95% CI: 1.45-2.11; p<0.001; I^2=0%; p<0.001). The RR increased over time from 1.53 (95% CI: 1.10-2.12; p=0.011) in 1991-1999 to 1.91 (95% CI: 1.43-2.54; p<0.001) in 2000-2009 (Figure 3). Pathogen-specific RR for attributable mortality was 1.60 (95% CI: 1.18-2.15; p=0.002) for *K. pneumoniae* and 1.76 (95% CI: 1.33-2.34; p<0.001) when the gram-negative organisms were analysed all together without species differentiation. The subgroup analysis showed the RR was lower in case cohort studies (1.56; 95% CI: 1.09-2.25; p=0.016) than in cohort studies (1.80; 95% CI: 1.37-2.37; p<0.001).

Length of stay

LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive) analysing 38 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95% CI: 3.37-5.46; p<0.001) and decreased from 5.72 days (95% CI: 2.69-8.75; p<0.001) in 1991-1999 to 4.22 days (95% CI: 3.02-5.43; p<0.001) in 2000-2009 and was stable up to 2018 (4.30 days; 95% CI: 1.38-7.22; p=0,004). Higher WMD (p<0.001) was observed for BSIs due to *K. pneumoniae* (7.67 days; 4.63-10.71) than for those due to *E. coli* (6.07 days; 95% CI 3.71-8.43). Retrospective cohort studies reported higher (p<0.001) WMD (6.43 days; 95% CI: 4.66-8.21; p<0.001) than case cohort studies (3.32 days; 95% CI: 2.03-4.61). Studies in HICs showed higher WMD (4.56 days; 95% CI 3.43-5.70; p<0.001) than studies in LMICs (3.55 days; 95% CI 0.84-6.26; p=0.01) (Figure 4).

Studies with non-invasive infections reported a WMD of 2.19 days (95% CI: 1.56-2.81; p<0.001), which decreased from 7.66 (95% CI: 5.83-9.46; p<0.001) in 2000-2009 to 1.44 (95% CI: 0.77-2.10; p<0.001) in 2010-2018 (online supplementary figure 7).

The data on ICU-LOS were provided in 7 studies and showed that BSIs caused by ESBL producers had a WMD of LOS of 3.07 days (95% CI: 1.61-4.54; p<0.001).

Heterogeniety of the studied effect-modifiers did not reach statistical significance when assessed by metaregression (supplementary table S6). Sensitivity analysis based on the quality of studies revealed no notable difference in the effect estimates after exclusion of low-quality studies (data not shown). Egger's test and the funnel plots (online supplementary figure 1 and 2) showed evidence for small study effects (p<0.001) and publication bias.

DISCUSSION

This systematic review shows that ESBL production has a significant impact on the most relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality, attributable mortality, and LOS both in hospital and in ICU were higher for patients with BSIs due to ESBL-producing *Enterobacteriaceae* than for patients with BSIs due to non-ESBL-producing strains. Non-invasive infections caused by ESBL-producing strains were associated with higher all-cause mortality and prolonged LOS. Within the limitation of the low number of studies evaluating specific patient populations, paediatric and cancer patients seemed to suffer a higher impact of ESBL invasive infections than the overall population. Stratifying by pathogen type, the impact of ESBL production was higher for *E. coli* BSIs than for *K. pneumoniae* BSIs. No relevant differences in mortality analysis emerged with stratification by study design or country income level. Impact of ESBL infections on mortality became more evident in more recent studies. Studies reporting on appropriateness of empirical therapy, ESBL resistance mechanisms, and MICs showed a higher clinical impact of ESBL infections than studies not assessing these variables. In particular, pooled ORs adjusted for inappropriate empirical treatment, showed a remarkably higher OR for mortality in patients with ESBL infections.

Our findings confirm the results of previous systematic reviews. Schwaber et al. performed a systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies published through 2003.[2] The authors show a pooled RR for all-cause mortality of 1.85 but, in contrast to our study, they combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in the analysis because of sample size limitations. Rottier et al. analysed studies published through 2010 and adjusting results for inappropriate empirical treatment found an adjusted OR of 1.37.[3] Our study, adding more than 50 studies in 17 years to the Rottier systematic review, confirmed the clinical importance of ESBL production to all-cause mortality and for the first time assessed the role of ESBL production on attributable mortality. We addressed relevant effect-modifiers

through subgroup analyses and found that population, pathogen, and assessment of empiric therapy all had an impact on estimates. Because we believe that appropriate empirical treatment plays a relevant role in invasive infections, we performed a secondary analysis by pooling only adjusted ORs and confirming the significant impact of antibiotic resistance as already shown in a previously published systematic review.[97] The lack of consideration of appropriateness of therapy in the studies evaluating mortality seems to underestimate the impact of ESBL production on mortality. However, studies assessing the impact of appropriate therapy did not provide homogeneous definition and could refer either to empirical or definite therapy or a single component irrespective of the dosage, making results difficult to interpret. Especially in infections with different sources and different clinical severity, the sole contribution of empirical therapy remains challenging to measure. For example, patients with UTI receiving inappropriate empirical antibiotic therapy can potentially show a favourable outcome, most probably due to the high concentration of antibiotic reached in the urinary tract.[98]

Community acquired ESBL infections emerged in the late 1990s and show an increasing trend.[99,100] Recent study shows that community onset ESBL infections are associated with lower mortality compared with healthcare associated and hospital acquired infections.[101] The place of acquisition could not be appropriately addressed in our meta-analysis due to the lack of data in included studies.

Our systematic review contributes to the discussion on the limitation of current evidence for the estimation of mortality due to antibiotic-resistant infections. The impact of ESBL production on LOS in our study has shown that both BSIs and non-invasive infections lead to prolongation of hospitalisation.

Our study has some limitations. Although results of the meta-analyses were significant in all the subgroups, we could analyse only a limited number of studies providing information for subgroups such as haematological patients and low-income countries, making generalizability of results less certain for these specific patient populations. Only a few studies reported MIC data or specific ESBL molecular resistant phenotype (i.e., AmpC). Moreover, publication bias was detected in both the main analyses (all-cause mortality and LOS), thus implying the possibility that results from small studies with non-significant results might have been conducted and not published, resulting in a possible overestimation of our results. The non-homogeneous reporting of some relevant data in published literature (e.g., disease severity,

underlying comorbidities and resistance mechanism) may also have affected the precision of the estimate. Patients with ESBL are intrinsically at higher risk of mortality and complications because they are often older, have more comorbidities or higher antibiotic exposure, and are at higher risk of receiving inappropriate empirical treatment.[102] Finally, due to resource constraints, we had to limit our search to PubMed database with the chance of missing relevant studies.

In summary, our systematic review emphasises the importance of suspicion and confirmation of ESBL production as soon as possible for invasive infections and demonstrates that ESBL production increases the risk of attributable mortality and LOS in both hospital and ICU for invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of mortality and prolonged LOS even after adjustment for empiric inappropriate treatment. Control for other relevant effect-modifiers is hindered by the sparseness of published data. Individual patient data (IPD) network meta-analyses are needed to define differences in outcomes between severe intravascular infections and bacteremia. Future studies addressing the clinical burden of drug-resistant infections must include ESBL production and should assess both the impact of molecular mechanisms of resistance and effect on specific patient populations such as haematological patients and those in LMIC.

Acknowledgements We thank Anne McDonough, a professional medical writer who provided medical writing support funded by the authors.

Author Contributions ET contributed to the study concept. BPG and PS performed data analysis. PS and AC extracted data and wrote the first draft of the manuscript. DL contributed to the first draft of the manuscript. EC and ET wrote the final version of the manuscript. CB reviewed the paper. All authors read, edited, and approved the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding This work was supported by the German Center for Infection Research Clinical Research Unit for Health-Care Associated Infections grant number TTU 08.701 and DRIVE-AB (115618). The funder had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Competing interests The authors report no competing interests.

Patient consent Not required

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Requests for data should be addressed to the corresponding author.

REFERENCES

1. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 2018;18:318–27.
2. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:913–20.
3. Rottier WC, Ammerlaan HS, Bonten MJ. Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. *J Antimicrob Chemother* 2012;67:1311–20.
4. Cassini A, Högberg LD, Plachouras D, et al; Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;19:56–66.
5. The World Bank. What is the World Bank Atlas method? https://datahelpdesk.worldbank.org/knowledgebase/articles/77933-what-is-the-world-bank-atlas-method. Accessed January 14, 2019.
6. Rodriguez-Bano J, Gutierrez-Gutierrez B, Machuca I et al. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clin Microbiol Rev 2018; 31. doi:10.1128/CMR.00079-17
7. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M *et al*. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. The Ottawa Health Research Institute: Ottawa, Canada. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed April 14 2015
8. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
9. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
10. Lautenbach E, Patel JB, Bilker WB, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *Clin Infect Dis* 2001;32:1162–71.

11. Leistner R, Sakellariou C, Gurntke S, et al. Mortality and molecular epidemiology associated with extended-spectrum beta-lactamase production in Escherichia coli from bloodstream infection. *Infect Drug Resist* 2014;7:57–62.
12. Lin JN, Chen YH, Chang LL, et al. Clinical characteristics and outcomes of patients with extended-spectrum beta-lactamase-producing bacteremias in the emergency department. *Intern Emerg Med* 2011;6:547–55.
13. Kim HJ, Park JH, Park DI, et al. Clinical impact of extended-spectrum beta-lactamase-producing Enterobacteriaceae in patients with biliary tract infection. *Dig Dis Sci* 2013;58:841–9.
14. Kim SH, Kwon JC, Choi SM, et al. Escherichia coli and Klebsiella pneumoniae bacteremia in patients with neutropenic fever: factors associated with extended-spectrum beta-lactamase production and its impact on outcome. *Ann Hematol* 2013;92:533–41.
15. Pillay T, Pillay DG, Adhikari M, et al. Piperacillin/tazobactam in the treatment of Klebsiella pneumoniae infections in neonates. *Am J Perinatol* 1998;15:47–51.
16. Kim BN, Woo JH, Kim MN, et al. Clinical implications of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae bacteraemia. *J Hosp Infect* 2002;52:99–106.
17. Kim YK, Pai H, Lee HJ, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in children: epidemiology and clinical outcome. *Antimicrob Agents Chemother* 2002;46:1481–91.
18. Bhavnani SM, Ambrose PG, Craig WA, et al. Outcomes evaluation of patients with ESBL- and non-ESBL-producing Escherichia coli and Klebsiella species as defined by CLSI reference methods: report from the SENTRY Antimicrobial Surveillance Program. *Diagn Microbiol Infect Dis* 2006;54:231–6.
19. Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol* 2005;43:745–9.
20. Panhotra BR, Saxena AK, Al-Ghamdi AM. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae hospital acquired bacteremia. Risk factors and clinical outcome. *Saudi Med J* 2004;25:1871–6.
21. Marra AR, Wey SB, Castelo A, et al. Nosocomial bloodstream infections caused by Klebsiella pneumoniae: impact of extended-spectrum beta-lactamase (ESBL) production on clinical outcome in a hospital with high ESBL prevalence. *BMC Infect Dis* 2006;6:24.

22. Skippen I, Shemko M, Turton J, et al. Epidemiology of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp.: a nested case-control study from a tertiary hospital in London. *J Hosp Infect* 2006;64:115–23.
23. Schwaber MJ, Navon-Venezia S, Kaye KS, et al. Clinical and economic impact of bacteremia with extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2006;50:1257–62.
24. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Clinical and molecular epidemiology of community-onset, extended-spectrum beta-lactamase-producing Escherichia coli infections in Thailand: a case-case-control study. *Am J Infect Control* 2007;35:606–12.
25. Tumbarello M, Spanu T, Sanguinetti M, et al. Bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae: risk factors, molecular epidemiology, and clinical outcome. *Antimicrob Agents Chemother* 2006;50:498–504.
26. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Risk factors for and outcomes of healthcare-associated infection due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae in Thailand. *Infect Control Hosp Epidemiol* 2007;28:873–6. doi: 10.1086/518725
27. Kanafani ZA, Mehio-Sibai A, Araj GF, et al. Epidemiology and risk factors for extended-spectrum beta-lactamase-producing organisms: a case control study at a tertiary care center in Lebanon. *Am J Infect Control* 2005;33:326–32.
28. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in children. *Pediatrics* 2005;115:942–9.
29. Loh LC, Nor Izran Hanim Bt Abdul S, Rosdara Masayuni Bt Mohd S, et al. Hospital Outcomes of Adult Respiratory Tract Infections with Extended-Spectrum B-Lactamase (ESBL) Producing Klebsiella Pneumoniae. *Malays J Med Sci* 2007;14:36–40.
30. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing E. coli compared to non-ESBL producing E. coli. *J Infect* 2007;55:254–9. doi: 10.1016/j.jinf.2007.04.007
31. Song KH, Jeon JH, Park WB, et al. Clinical outcomes of spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species: a retrospective matched case-control study. *BMC Infect Dis* 2009;9:41.
32. Bennett JW, Robertson JL, Hospenthal DR, et al. Impact of extended spectrum beta-lactamase producing Klebsiella pneumoniae infections in severely burned patients. *J Am Coll Surg* 2010;211:391–9.

33. Trecarichi EM, Tumbarello M, Spanu T, et al. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by Escherichia coli in patients with hematological malignancies. *J Infect* 2009;58:299–307.
34. Tuon FF, Kruger M, Terreri M, et al. Klebsiella ESBL bacteremia-mortality and risk factors. *Braz J Infect Dis* 2011;15:594–8.
35. Kang CI, Song JH, Chung DR, et al. Risk factors and treatment outcomes of community-onset bacteraemia caused by extended-spectrum beta-lactamase-producing Escherichia coli. *Int J Antimicrob Agents* 2010;36:284–7.
36. Pena C, Gudiol C, Calatayud L, et al. Infections due to Escherichia coli producing extended-spectrum beta-lactamase among hospitalised patients: factors influencing mortality. *J Hosp Infect* 2008;68:116–22.
37. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. *Antimicrob Agents Chemother* 2010;54:4085–91.
38. Kang CI, Chung DR, Ko KS, et al. Risk factors for infection and treatment outcome of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in patients with hematologic malignancy. *Ann Hematol* 2012;91:115–21.
39. Wu YH, Chen PL, Hung YP, et al. Risk factors and clinical impact of levofloxacin or cefazolin nonsusceptibility or ESBL production among uropathogens in adults with community-onset urinary tract infections. *J Microbiol Immunol Infect* 2014;47:197–203.
40. Rodriguez-Bano J, Picon E, Gijon P, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli: risk factors and prognosis. *Clin Infect Dis* 2010;50:40–8.
41. Gurntke S, Kohler C, Steinmetz I, et al. Molecular epidemiology of extended-spectrum beta-lactamase (ESBL)-positive Klebsiella pneumoniae from bloodstream infections and risk factors for mortality. *J Infect Chemother* 2014;20:817–9.
42. Oh MM, Chae JY, Kim JW, et al. Positive culture for extended-spectrum beta-lactamase during acute prostatitis after prostate biopsy is a risk factor for progression to chronic prostatitis. *Urology* 2013;81:1209–12.
43. Leistner R, Gurntke S, Sakellariou C, et al. Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive K. pneumoniae and E. coli: an analysis of the disease burden in a large cohort. *Infection* 2014;42:991–7.

44. Ku NS, Chung HS, Choi JY, et al. Clinical usefulness of the 2010 clinical and laboratory standards institute revised breakpoints for cephalosporin use in the treatment of bacteremia caused by Escherichia coli or Klebsiella spp. *Biomed Res Int* 2015;2015:831074.
45. Anunnatsiri S, Towiwat P, Chaimanee P. Risk factors and clinical outcomes of extended spectrum beta-lactamase (ESBL)-producing Escherichia coli septicemia at Srinagarind University Hospital, Thailand. *Southeast Asian J Trop Med Public Health* 2012;43:1169–77.
46. Kang CI, Kim SH, Kim DM, et al. Risk factors for and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae. *Infect Control Hosp Epidemiol* 2004;25:860–7.
47. Raviv Y, Shitrit D, Amital A, et al. Multidrug-resistant Klebsiella pneumoniae acquisition in lung transplant recipients. *Clin Transplant* 2012;26:E388–94.
48. MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. *J Hosp Med* 2014;9:232–8.
49. Abhilash KP, Veeraraghavan B, Abraham OC. Epidemiology and outcome of bacteremia caused by extended spectrum beta-lactamase (ESBL)-producing Escherichia coli and Klebsiella spp. in a tertiary care teaching hospital in south India. *J Assoc Physicians India* 2010;58 Suppl:13-7.
50. Shanthi M, Sekar U. Extended spectrum beta lactamase producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *J Assoc Physicians India* 2010;58 Suppl:41–4.
51. Han SB, Jung SW, Bae EY, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in febrile neutropenic children. *Microb Drug Resist* 2015;21:244–51.
52. Lee S, Song DY, Cho SH, et al. Impact of extended-spectrum beta-lactamase on acute pyelonephritis treated with empirical ceftriaxone. *Microb Drug Resist* 2014;20:39–44.
53. Chayakulkeeree M, Junsriwong P, Keerasuntonpong A, et al. Epidemiology of extended-spectrum beta-lactamase producing gram-negative bacilli at Siriraj Hospital, Thailand, 2003. *Southeast Asian J Trop Med Public Health* 2005;36:1503–9.
54. Apisarnthanarak A, Kiratisin P, Mundy LM. Predictors of mortality from community-onset bloodstream infections due to extended-spectrum beta-lactamase-producing

Escherichia coli and Klebsiella pneumoniae. *Infect Control Hosp Epidemiol* 2008;29:671–4.

55. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Predictors of mortality among patients with community-onset infection due to extended-spectrum beta-lactamase-producing Escherichia coli in Thailand. *Infect Control Hosp Epidemiol* 2008;29:80–2.
56. Jean SS, Ko WC, Xie Y, et al. Clinical characteristics of patients with community-acquired complicated intra-abdominal infections: a prospective, multicentre, observational study. *Int J Antimicrob Agents* 2014;44:222–8.
57. Lee J, Pai H, Kim YK, et al. Control of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a children's hospital by changing antimicrobial agent usage policy. *J Antimicrob Chemother* 2007;60:629–37.
58. Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, et al. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. *Int J Clin Pract* 2012;66:891–6.
59. Ha YE, Kang CI, Cha MK, et al. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in patients with cancer. *Int J Antimicrob Agents* 2013;42:403–9.
60. Du B, Long Y, Liu H, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bloodstream infection: risk factors and clinical outcome. *Intensive Care Med* 2002;28:1718–23.
61. Stone PW, Gupta A, Loughrey M, et al. Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae outbreak in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2003;24:601–6.
62. Pena C, Pujol M, Ardanuy C, et al. An outbreak of hospital-acquired Klebsiella pneumoniae bacteraemia, including strains producing extended-spectrum beta-lactamase. *J Hosp Infect* 2001;47:53–9.
63. Kola A, Maciejewski O, Sohr D, et al. Clinical impact of infections caused by ESBL-producing E. coli and K. pneumoniae. *Scand J Infect Dis* 2007;39:975–82.
64. Tsai MH, Lee IT, Chu SM, et al. Clinical and Molecular Characteristics of Neonatal Extended-Spectrum beta-Lactamase-Producing Gram-Negative Bacteremia: A 12-Year Case-Control-Control Study of a Referral Center in Taiwan. *PLoS One* 2016;11(8):e0159744.

65. Maslikowska JA, Walker SA, Elligsen M, et al. Impact of infection with extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella species on outcome and hospitalization costs. *J Hosp Infect* 2016;92:33–41.
66. Onken A, Said AK, Jorstad M, et al. Prevalence and antimicrobial resistance of microbes causing bloodstream infections in Unguja, Zanzibar. *PLoS One* 2015;10:e0145632.
67. Nguyen ML, Toye B, Kanji S, et al. Risk factors for and outcomes of bacteremia caused by extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella species at a Canadian tertiary care hospital. *Can J Hosp Pharm* 2015;68(2):136–43. [published Online First: 2015/05/13]
68. Denis B, Lafaurie M, Donay JL, et al. Prevalence, risk factors, and impact on clinical outcome of extended-spectrum beta-lactamase-producing Escherichia coli bacteraemia: a five-year study. Int *J Infect Dis* 2015;39:1–6.
69. Chopra T, Marchaim D, Johnson PC, et al. Risk factors for bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: A focus on antimicrobials including cefepime. *Am J Infect Control* 2015;43:719–23.
70. Artero A, Esparcia A, Alberola J, et al. Prospective cohort study of risk factors for extended-spectrum ss-lactamase-producing Escherichia coli urinary tract infections in elderly patients admitted to hospital. *Int J Clin Pract* 2017;71:doi:10.1111/ijcp.13001
71. Chen IL, Huang HC, Wu CT, et al. Analysis of early-onset bloodstream infection due to Escherichia coli infection in premature babies. *Medicine* 2017;96:e7748.
72. Islas-Munoz B, Volkow-Fernandez P, Ibanes-Gutierrez C, et al. Bloodstream infections in cancer patients. Risk factors associated with mortality. *Int J Infect Dis* 2018;71:59–64.
73. Ma J, Li N, Liu Y, et al. Antimicrobial resistance patterns, clinical features, and risk factors for septic shock and death of nosocomial E coli bacteremia in adult patients with hematological disease: A monocenter retrospective study in China. *Medicine* 2017;96:e6959.
74. Man MY, Shum HP, Chan YH, et al. Clinical predictors and outcomes of Klebsiella pneumoniae bacteraemia in a regional hospital in Hong Kong. *J Hosp Infect* 2017;97:35–41.
75. Marando R, Seni J, Mirambo MM, et al. Predictors of the extended-spectrum-beta lactamases producing Enterobacteriaceae neonatal sepsis at a tertiary hospital, Tanzania. *Int J Med Microbiol* 2018;308:803–11.

76. Namikawa H, Yamada K, Fujimoto H, et al. Clinical characteristics of bacteremia caused by extended-spectrum beta-lactamase-producing Escherichia coli at a tertiary hospital. *Intern Med* 2017;56:1807–15.
77. Shi SH, Feng XN, Lai MC, et al. Biliary diseases as main causes of pyogenic liver abscess caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Liver Int* 2017;37:727–34.
78. Tanir Basaranoglu S, Ozsurekci Y, Aykac K, et al. A comparison of blood stream infections with extended spectrum beta-lactamase-producing and non-producing Klebsiella pneumoniae in pediatric patients. *Ital J Pediat* 2 017;43:79.
79. Razazi K, Mekontso Dessap A, Carteaux G, et al. Frequency, associated factors and outcome of multi-drug-resistant intensive care unit-acquired pneumonia among patients colonized with extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Ann Intensive Care* 2017;7:61.
80. Ray S, Anand D, Purwar S, et al. Association of high mortality with extended-spectrum beta-lactamase (ESBL) positive cultures in community acquired infections. *J Crit Care* 2018;44:255–60.
81. Haruki Y, Hagiya H, Haruki M, et al. Clinical characteristics and outcome of critically ill patients with bacteremia caused by extended-spectrum beta-lactamase-producing and non-producing Escherichia coli. *J Infect Chemother* 2018;24:944–7.
82. Lin WT, Tang HJ, Lai CC, et al. Clinical manifestations and bacteriological features of culture-proven Gram-negative bacterial arthritis. *J Microbiol Immunol Infect* 2017;50:527–31.
83. Buys H, Muloiwa R, Bamford C, et al. Klebsiella pneumoniae bloodstream infections at a South African children's hospital 2006-2011, a cross-sectional study. BMC Infect Dis 2016;16:570.
84. Lee CC, Lee CH, Hong MY, et al. Propensity-matched analysis of the impact of extended-spectrum beta-lactamase production on adults with community-onset Escherichia coli, Klebsiella species, and Proteus mirabilis bacteremia. *J Microbiol Immunol Infect* 2018;51:519–26.
85. Huang YY, Alleyne A, Leung V, et al. Urosepsis due to extended-ppectrum beta-lactamase-producing Escherichia coli: a retrospective, single-centre review of risk Factors and clinical outcomes. *Can J Hosp Pharm* 2018;71:119-27.

86. Komatsu Y, Kasahara K, Inoue T, et al. Molecular epidemiology and clinical features of extended-spectrum beta-lactamase- or carbapenemase-producing Escherichia coli bacteremia in Japan. *PLoS One* 2018;13:e0202276.
87. Liu M, Li M, Wu L, et al. Extended-spectrum beta-lactamase-producing E. coli septicemia among rectal carriers in the ICU. *Medicine* 2018;97:e12445.
88. Nivesvivat T, Piyaraj P, Thunyaharn S, et al. Clinical epidemiology, risk factors and treatment outcomes of extended-spectrum beta-lactamase producing Enterobacteriaceae bacteremia among children in a tertiary care hospital, Bangkok, Thailand. *BMC Res Notes* 2018;11:624.
89. Cordery RJ, Roberts CH, Cooper SJ, et al. Evaluation of risk factors for the acquisition of bloodstream infections with extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in the intensive care unit; antibiotic management and clinical outcome. *J Hosp Infect* 2008;68:108–15.
90. Daikos GL, Kosmidis C, Tassios PT, et al. Enterobacteriaceae bloodstream infections: presence of integrons, risk factors, and outcome. *Antimicrob Agents Chemother* 2007;51:2366–72. doi: 10.1128/AAC.00044-07 [published Online First: 2007/04/25]
91. Gudiol C, Calatayud L, Garcia-Vidal C, et al. Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. *J Antimicrob Chemother* 2010;65(2):333–41.
92. Marchaim D, Gottesman T, Schwartz O, et al. National multicenter study of predictors and outcomes of bacteremia upon hospital admission caused by Enterobacteriaceae producing extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2010;54:5099–104.
93. Menashe G, Borer A, Yagupsky P, et al. Clinical significance and impact on mortality of extended-spectrum beta lactamase-producing Enterobacteriaceae isolates in nosocomial bacteremia. *Scand J Infect Dis* 2001;33:188–93.
94. Ortega M, Marco F, Soriano A, et al. Analysis of 4758 Escherichia coli bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. *J Antimicrob Chemother* 2009;63:568–74.
95. Szilagyi E, Fuzi M, Borocz K, et al. Risk factors and outcomes for bloodstream infections with extended-spectrum beta-lactamase-producing Klebsiella pneumoniae ; Findings of the nosocomial surveillance system in Hungary. *Acta Microbiol Immunol Hung* 2009;56:251–62. doi:

96. Tsai SS, Huang JC, Chen ST, et al. Characteristics of Klebsiella pneumoniae bacteremia in community-acquired and nosocomial infections in diabetic patients. *Chang Gung Med J* 2010;33:532–9.

97. Carrara E, Pfeffer I, Zusman O, et al. Determinants of inappropriate empirical antibiotic treatment: systematic review and meta-analysis. *Int J Antimicrob Agents* 2018;51:548–53,

98. Horcajada JP, Shaw E, Padilla B, et al. Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective multicentre cohort study in the era of antimicrobial resistance. *Clin Microbiol Infect*. 2013 Oct;19(10):96

99. Pitout JD, Nordmann P, Laupland KB et al. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. J Antimicrob Chemother 2005; 56: 52-59. doi:10.1093/jac/dki166

100. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 2008; 8: 159-166. doi:10.1016/S1473-3099(08)70041-0

101. Palacios-Baena ZR, Gutierrez-Gutierrez B, De Cueto M et al. Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-beta-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2017; 72: 906-913. doi:10.1093/jac/dkw513

102. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clin Microbiol Infect* 2014;20:973–80.

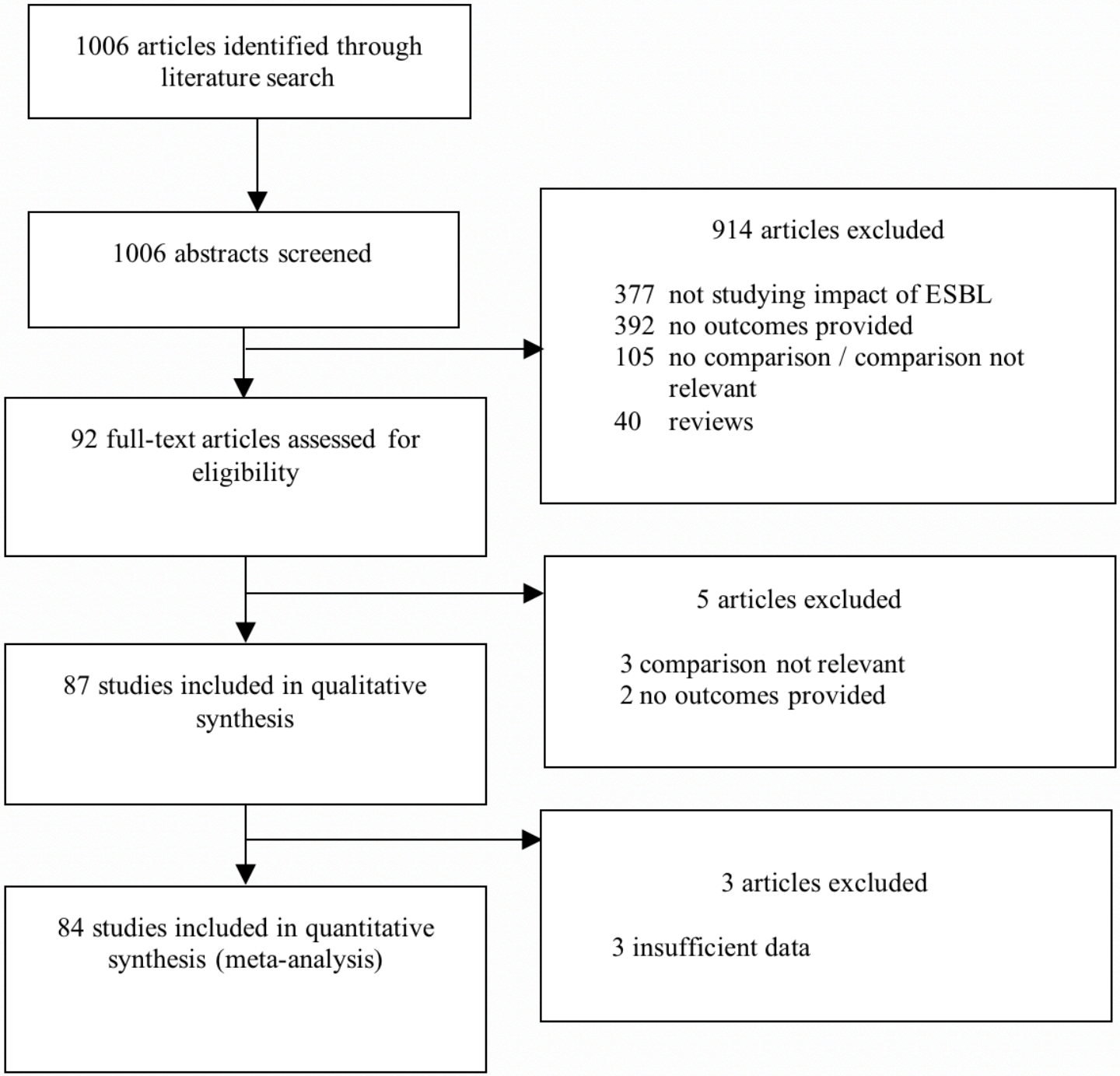
FIGURE LEGENDS

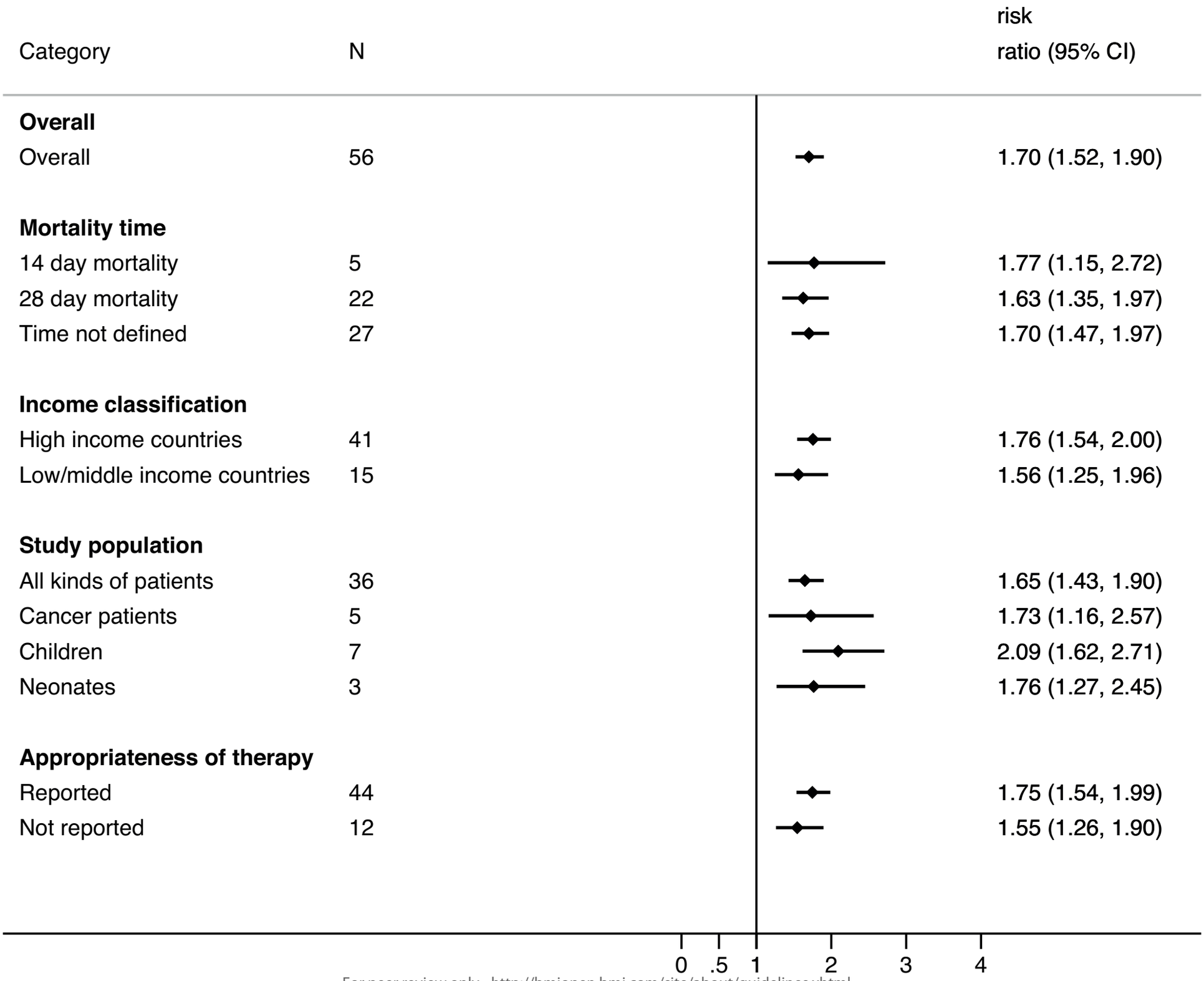
Figure 1: Literature search and study inclusion and exclusion

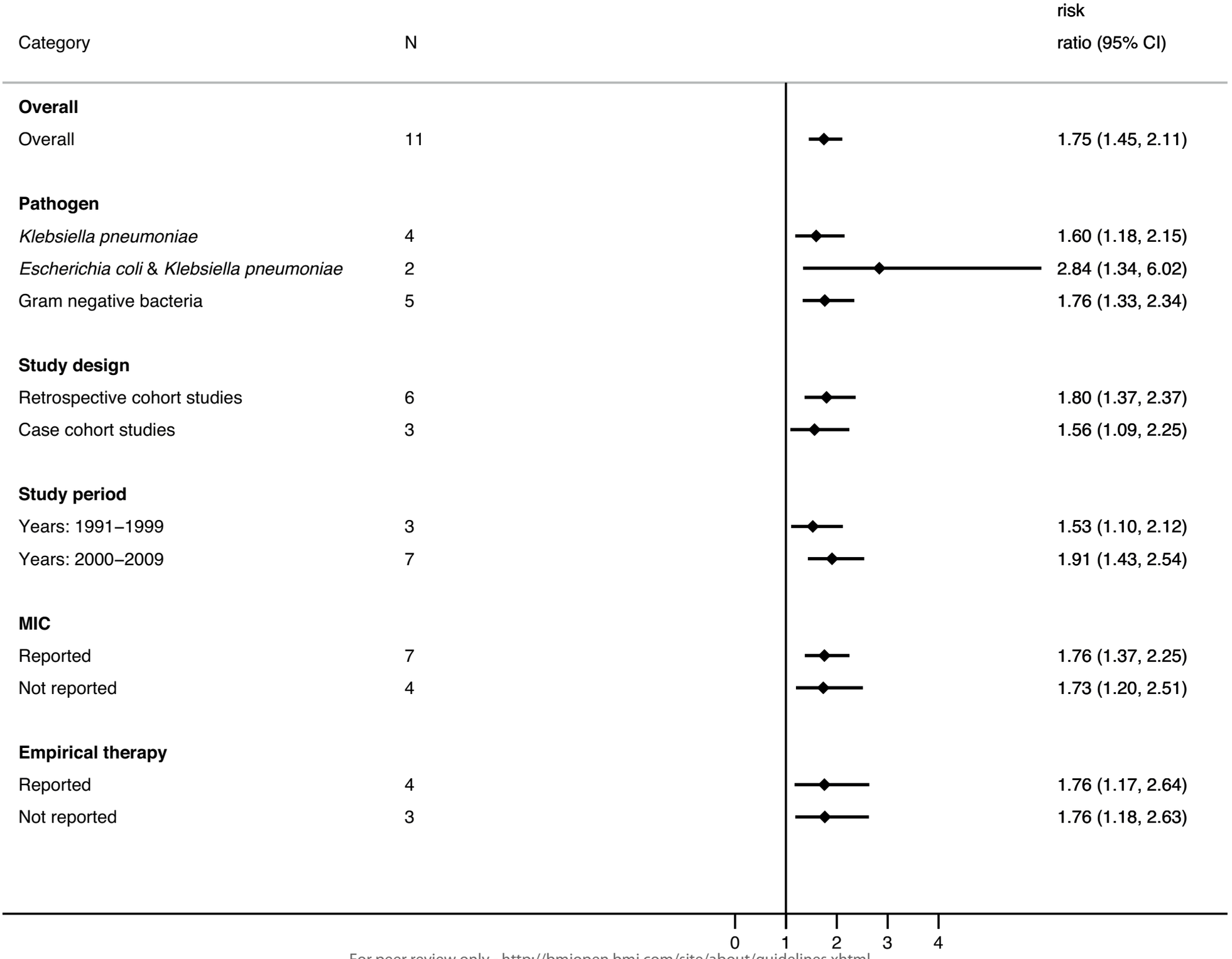
Figure 2: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections— subgroups not included in attributable mortality

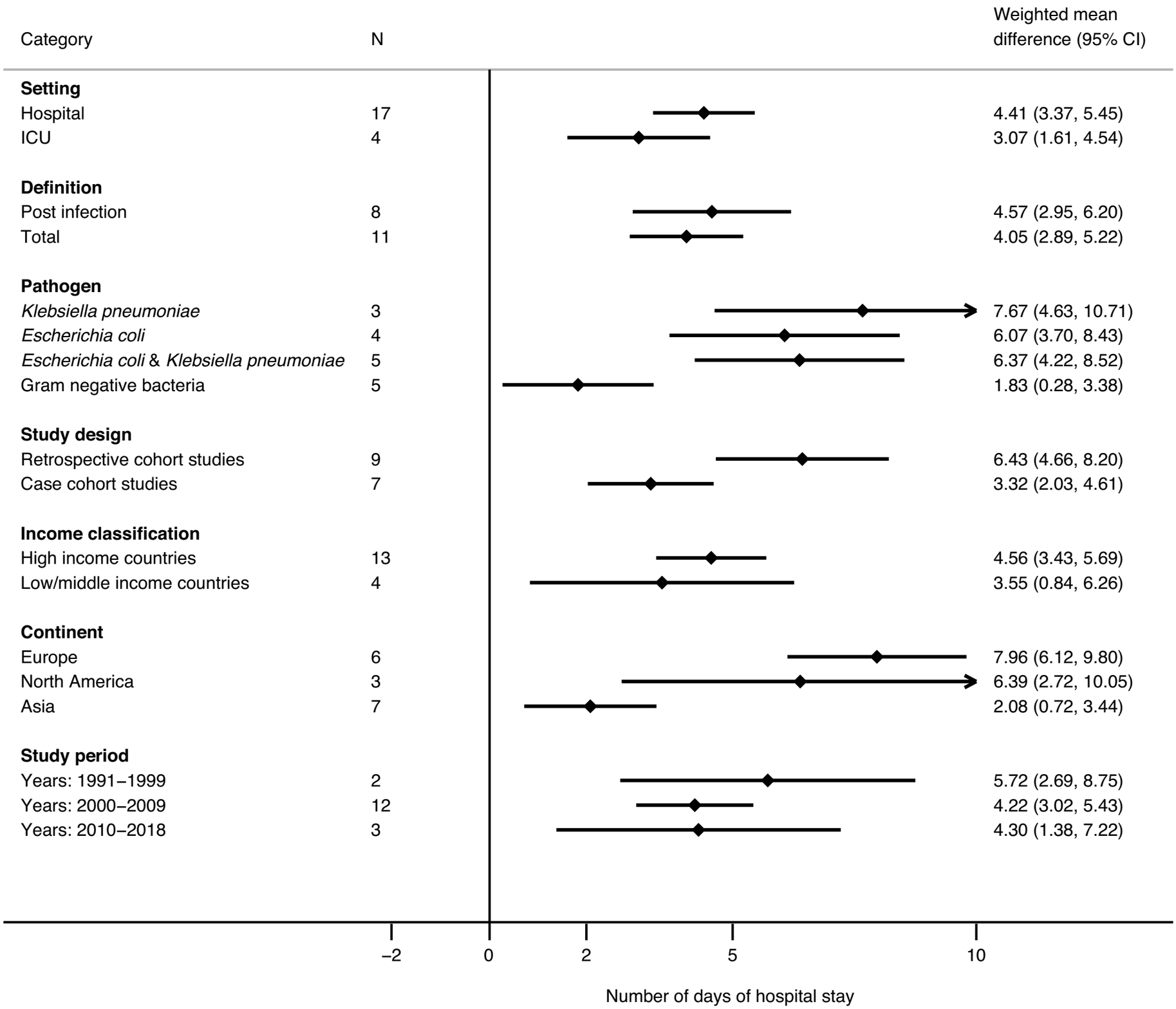
Figure 3: Pooled risk ratios for attributable mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

Figure 4: Weighted mean difference in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

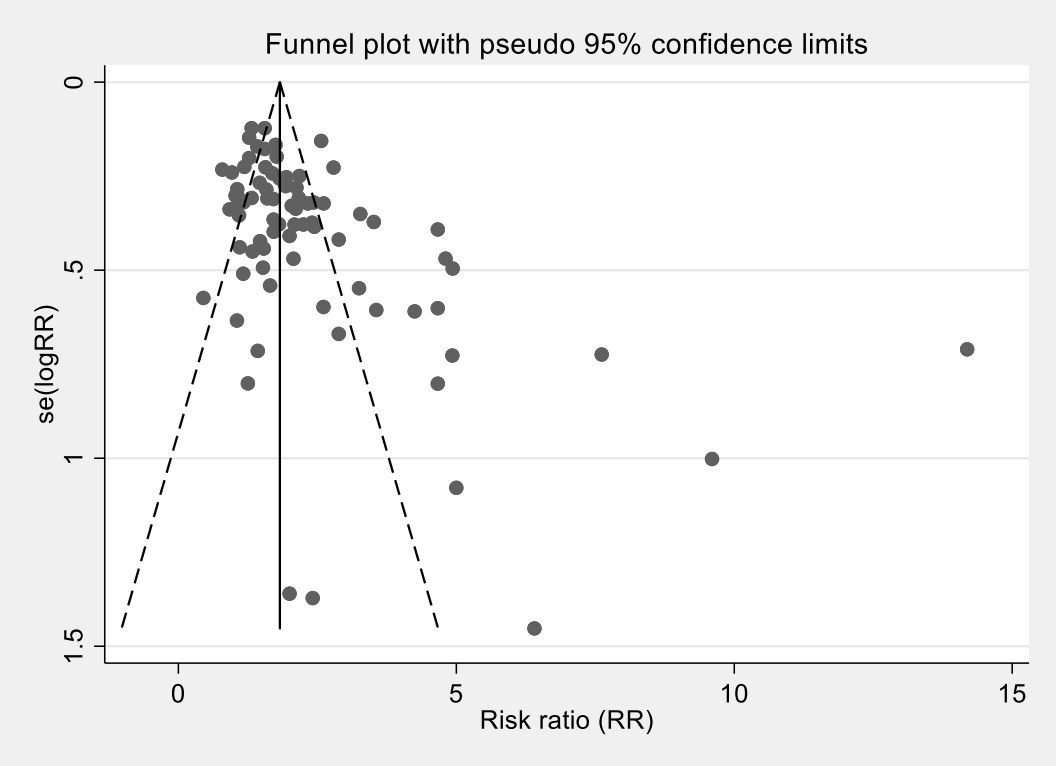

1006 articles identified through literature search
1006 abstracts screened
914 articles excluded
377 not studying impact of ESBL
392 no outcomes provided
105 no comparison / comparison not relevant
40 reviews
92 full-text articles assessed for eligibility
5 articles excluded
3 comparison not relevant
2 no outcomes provided
87 studies included in qualitative synthesis
3 articles excluded
3 insufficient data
84 studies included in quantitative synthesis (meta-analysis)




Category
N
risk ratio (95% CI)
Overall
Overall 11 1.75 (1.45, 2.11)
Pathogen
Klebsiella pneumoniae 4 1.60 (1.18, 2.15)
Escherichia coli & Klebsiella pneumoniae 2 2.84 (1.34, 6.02)
Gram negative bacteria 5 1.76 (1.33, 2.34)
Study design
Retrospective cohort studies 6 1.80 (1.37, 2.37)
Case cohort studies 3 1.56 (1.09, 2.25)
Study period
Years: 1991–1999 3 1.53 (1.10, 2.12)
Years: 2000–2009 7 1.91 (1.43, 2.54)
MIC
Reported 7 1.76 (1.37, 2.25)
Not reported 4 1.73 (1.20, 2.51)
Empirical therapy
Reported 4 1.76 (1.17, 2.64)
Not reported 3 1.76 (1.18, 2.63)
0
1
2
3
4

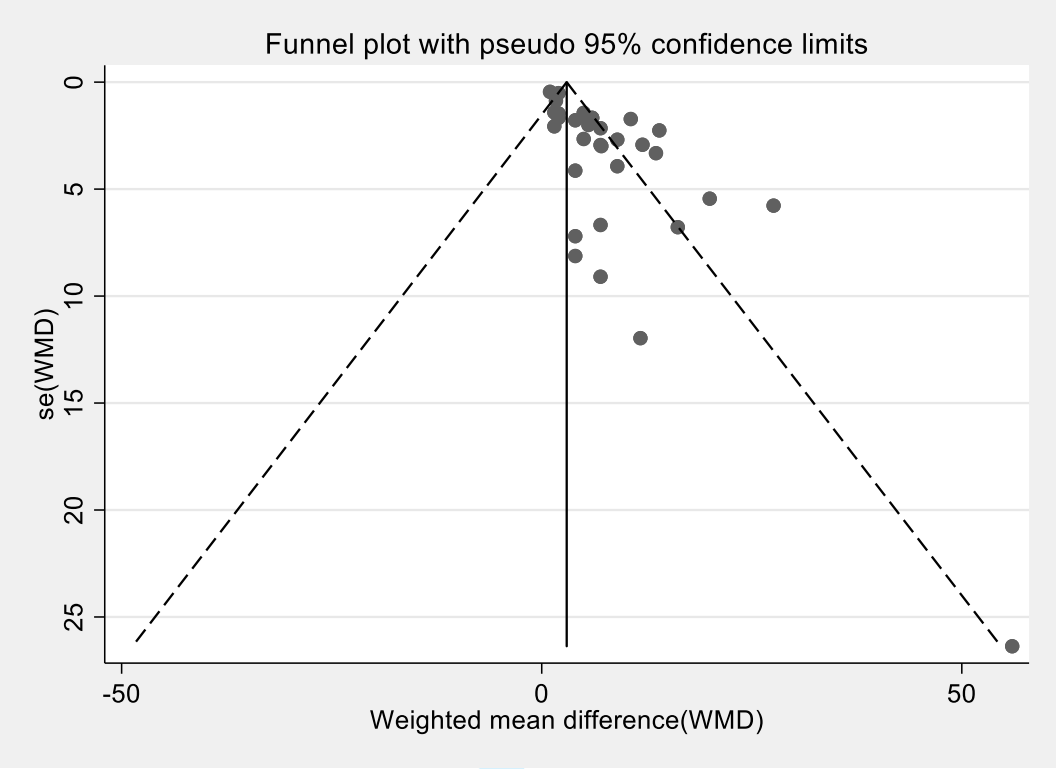

Category
N
Weighted mean difference (95% CI)
Setting
Hospital 17 4.41 (3.37, 5.45)
ICU 4 3.07 (1.61, 4.54)
Definition
Post infection 8 4.57 (2.95, 6.20)
Total 11 4.05 (2.89, 5.22)
Pathogen
Klebsiella pneumoniae 3 7.67 (4.63, 10.71)
Escherichia coli 4 6.07 (3.70, 8.43)
Escherichia coli & Klebsiella pneumoniae 5 6.37 (4.22, 8.52)
Gram negative bacteria 5 1.83 (0.28, 3.38)
Study design
Retrospective cohort studies 9 6.43 (4.66, 8.20)
Case cohort studies 7 3.32 (2.03, 4.61)
Income classification
High income countries 13 4.56 (3.43, 5.69)
Low/middle income countries 4 3.55 (0.84, 6.26)
Continent
Europe 6 7.96 (6.12, 9.80)
North America 3 6.39 (2.72, 10.05)
Asia 7 2.08 (0.72, 3.44)
Study period
Years: 1991–1999 2 5.72 (2.69, 8.75)
Years: 2000–2009 12 4.22 (3.02, 5.43)
Years: 2010–2018 3 4.30 (1.38, 7.22)
−2
0
2
5
10
Number of days of hospital stay

Supplementary figure 1: Funnel plot of risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



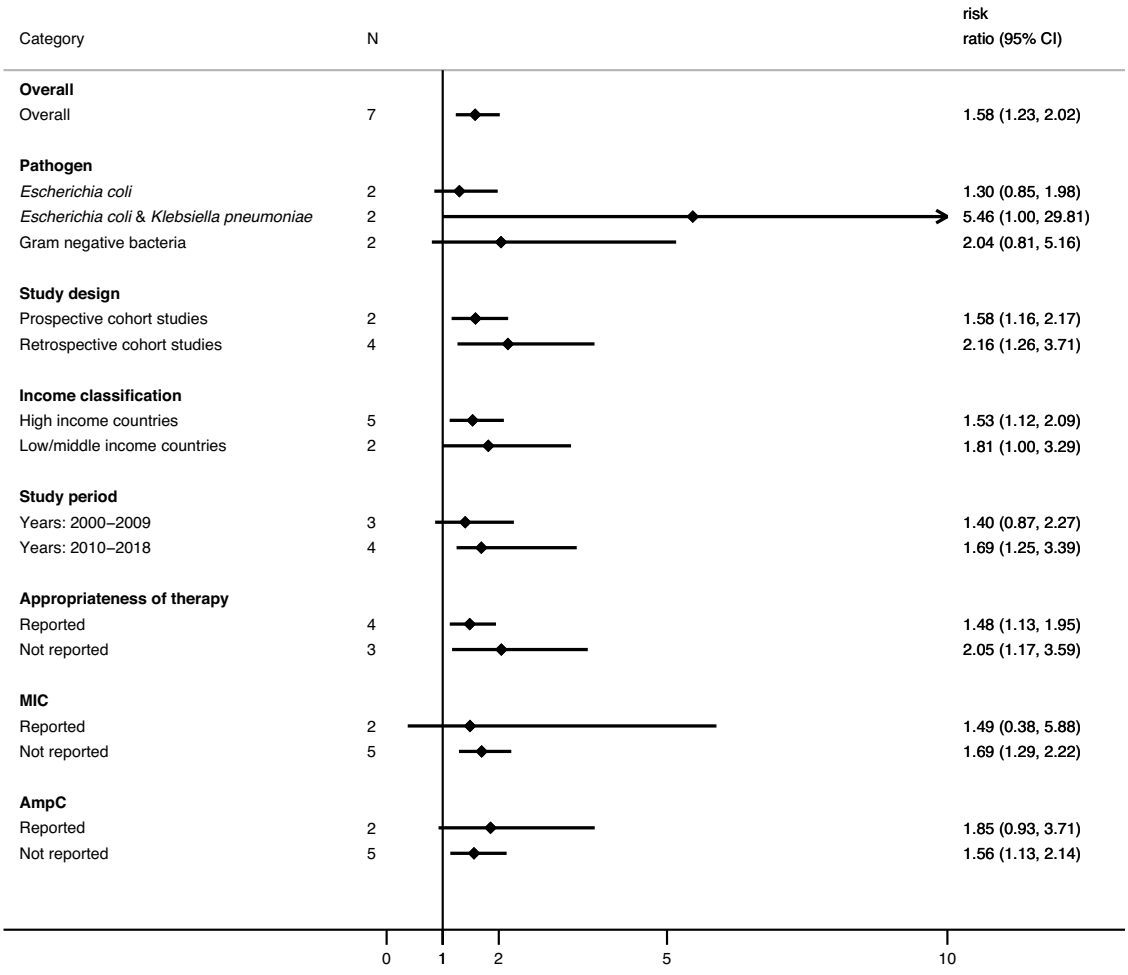
The y axis se(logRR) is the standard error of the log risk ratio Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 2: Funnel plot of weighted mean differences in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

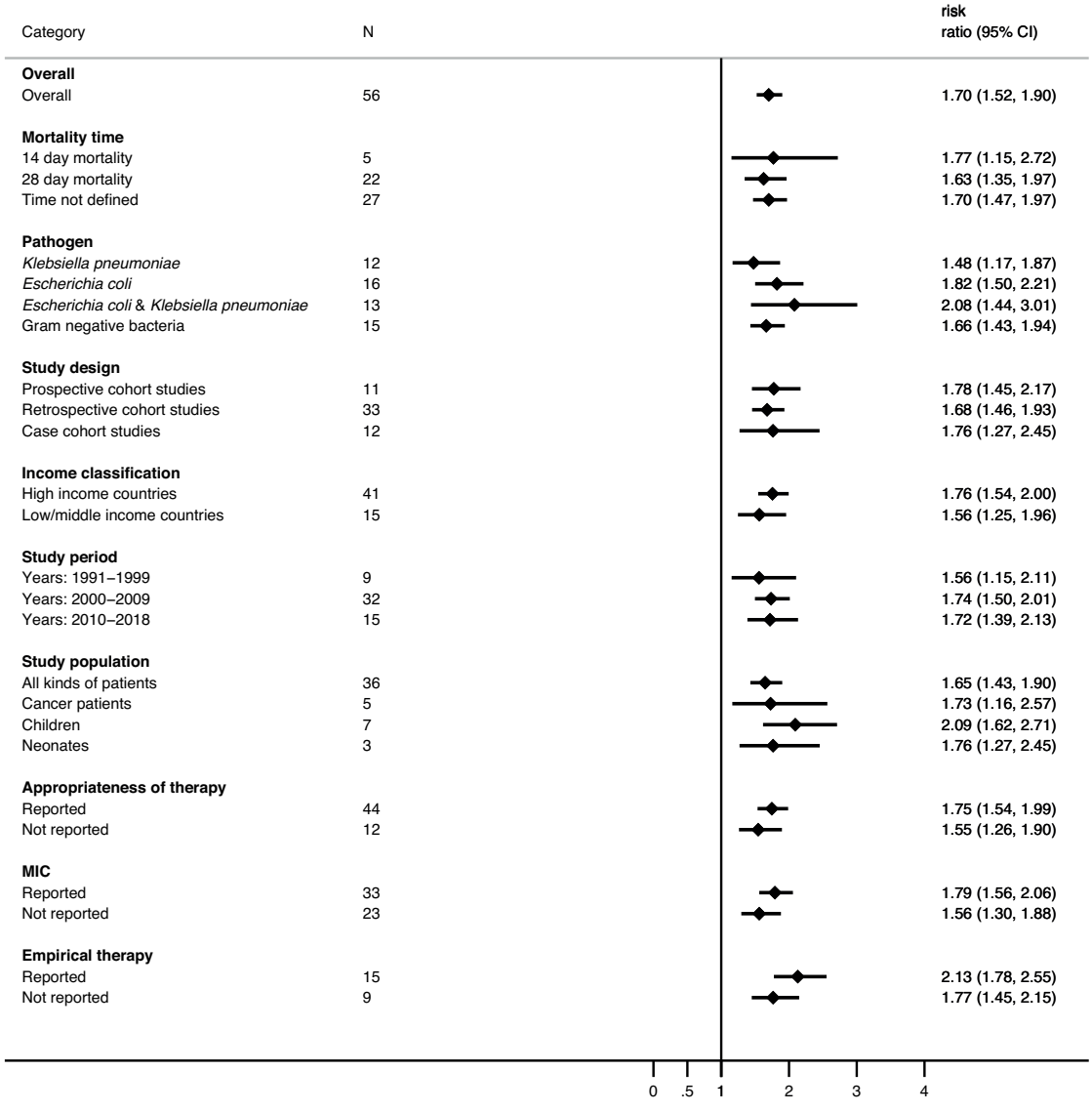


The y axis se(WMD) is the standard error of the weighted mean difference. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

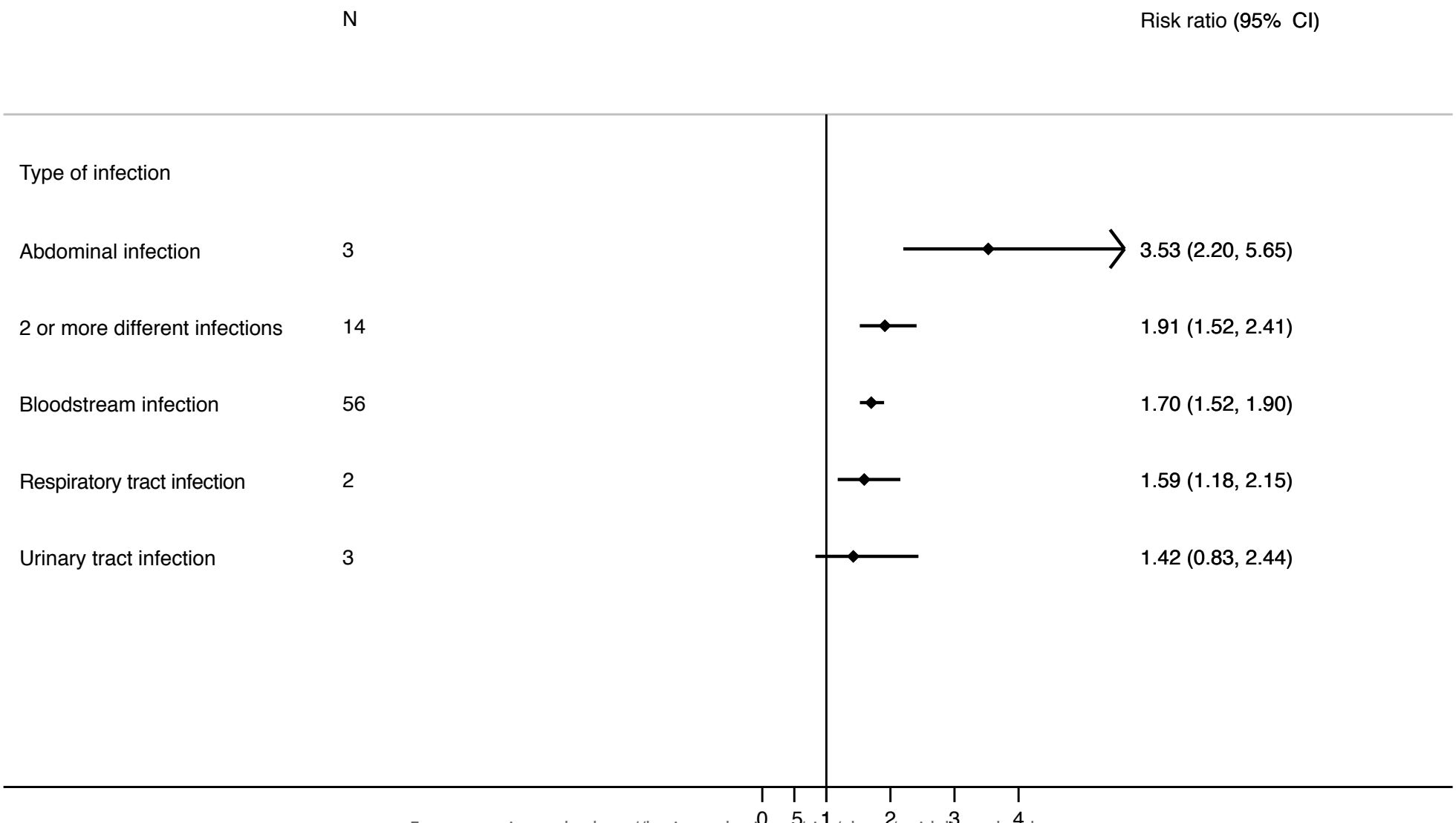
Supplementary figure 3: Pooled risk ratios for all-cause mortality in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



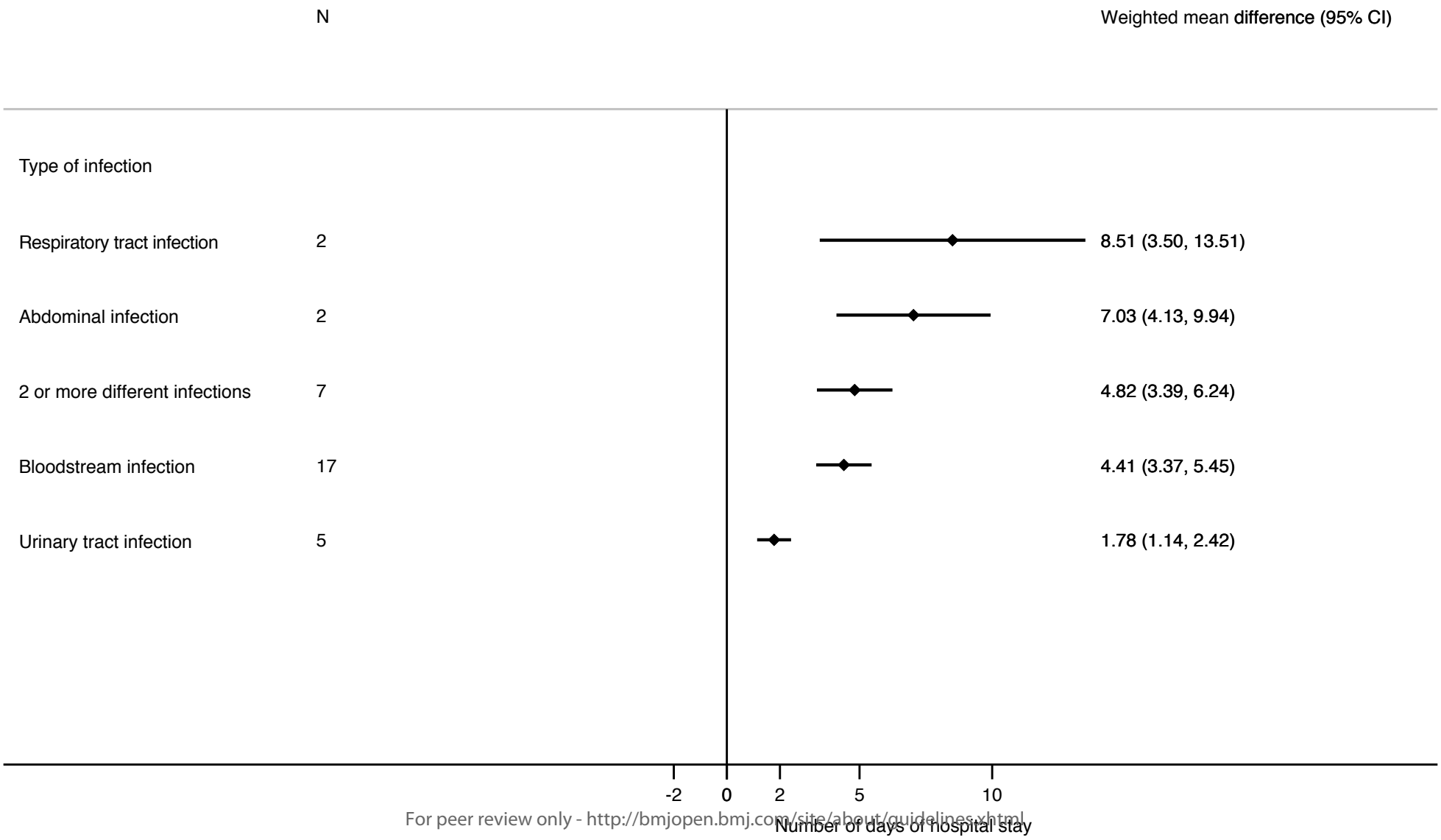
Supplementary figure 4: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections—all subgroups



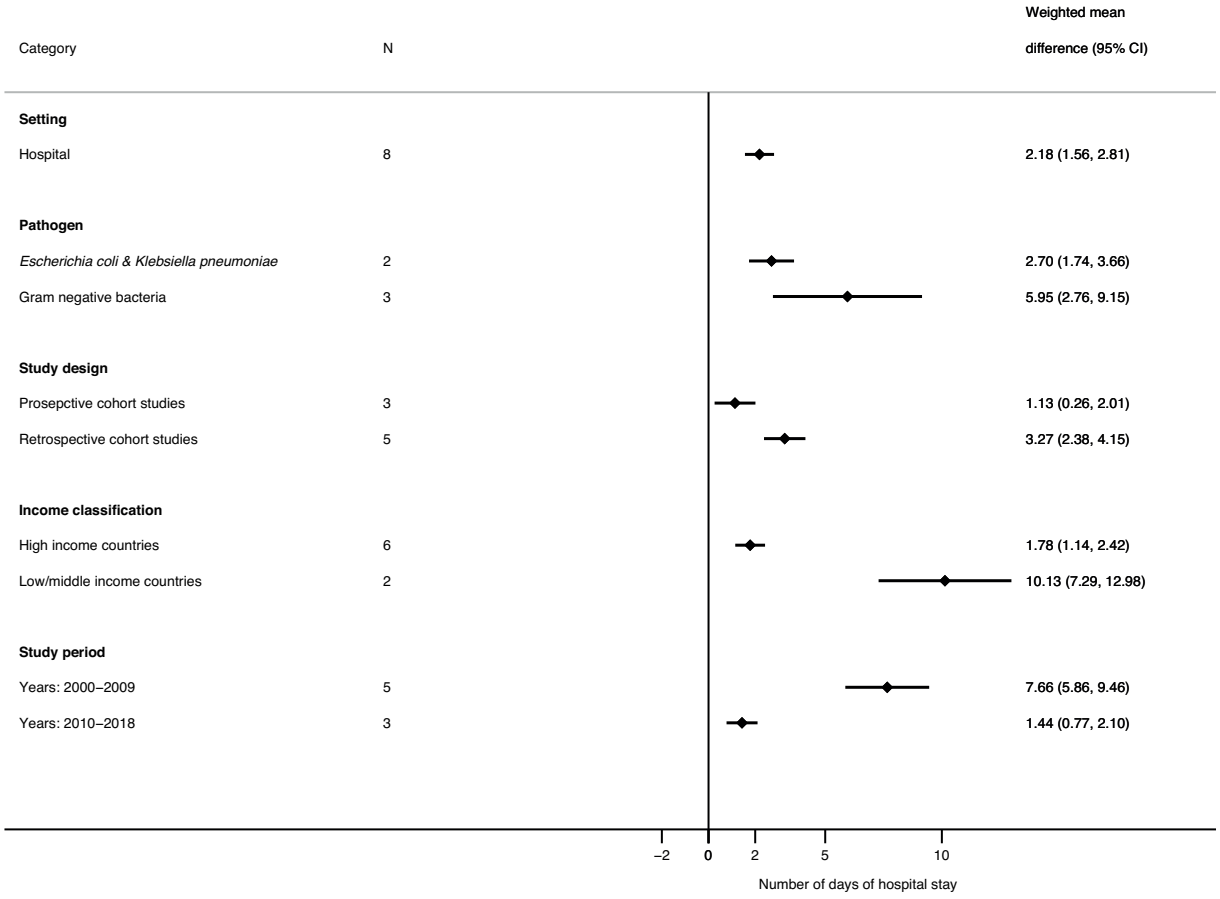
Supplementary figure 5: Pooled risk ratios for all-cause mortality stratified by type of infection



Supplementary figure 6: Weighted mean differences in length of hospital stay stratified by type of infection



Supplementary figure 7: Weighted mean differences in length of hospital stay in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary table S1: Search terms used in PubMed :

((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh])

AND

(Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])) OR (Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])

Coupled with

(length of stay[mesh] OR (hospitalisation[tw] AND length[tw]) OR length of hospitalisation[tw] OR length of hospitalization[tw] OR duration of hospitalization[tw] duration of hospitalisation[tw] OR LOS[tw] OR ((period[tw] OR length[tw]) AND (hospital stay[tw] OR hospitalisation[tw] OR hospitalization[tw]) OR

(mortality[mesh] OR mortality[tw] OR death rate[tw] OR fatality[tw] OR survival rate[tw] OR death[tw] OR died[tw] OR dead[tw])))) OR

(cost[Title/Abstract] OR"costs and cost analysis"[MeSH:noexp])*

Coupled with

("0001/01/01"[PDat] : "2018/10/01"[PDat]))

Supplementary table S2: Modified Newcastle Ottawa quality assessment scale for case-control studies and cohort studies.

	For case cohort studies, the quality criteria assessed are		
1	**Is the case definition adequate?**	a*	yes, with independent validation
		b	yes, eg. record linkage or based on self-report
		c	no description
2	**Representativeness of the cases**	a*	consecutive or obviously representative series of cases
		b	potential for selection biases or not stated
3	**Selection of Controls**	a*	community controls
		b	hospital controls
		c	no description
4	**Definition of Controls**	a*	no history of disease (endpoint)
		b	no description of source
5	**Comparability of cases and controls on the basis of the design or analysis**	a*	study controls for at least one variable (including age, sex and comorbidities)
		b**	study controls for more than one variable (including age, sex and comorbidities)
6	**Ascertainment of exposure**	a*	secure record (eg surgical records)
		b	structured interview blind to case/control status
		c	interview not blinded to case/control status
		d	written self-report or medical record only
		e	no description
7	**Same method of ascertainment for cases and controls**	a*	yes
		b	no
		c	unclear
8	**Non-Response rate**	a	same rate for both groups
		b	non respondents described
		c	rate different and no designation
	For cohort studies, the quality criteria assessed are		
1	**Representativeness of the exposed cohort**	a*	truly representative
		b*	somewhat representative
		c	selected group of users
		d	no description
2	**Selection of the non-exposed cohort**	a*	drawn from the same community as the exposed cohort
		b	drawn from a different source
		c	no description of the derivation of the non-exposed cohort
3	**Ascertainment of exposure**	a*	secure record (eg surgical records)
		a*	structured interview
		c	written self-report
		d	no description
4	**Demonstration that outcome of interest was not present at start of study**	a*	yes
		b	no
		c	unclear
5	**Comparability of cohorts on the basis of the design or analysis**	a*	study controls for age or comorbidities
		b**	study controls for age and comorbidities
6	**Assessment of outcome:**	a*	independent blind assessment
		b*	record linkage
		c	self-report
		d	no description

7	**Follow-up long enough for outcomes to occur**	a*	yes
		b	no
		c	unclear
8	**Adequacy of follow up of cohorts**	a*	complete follow up – all that matters subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number
		b*	inadequate numbers but description provided of those lost
		c	inadequate follow up rate and no description of those lost
		d	no statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Supplementary table S3: Study characteristics overview

Subgroup	All Studies	Bloodstream infections	Noninvasive infections
	87	**57**	**10**
Country			
South Korea [13,14,16,17,31,35,38,42,44,46,51,52,57,59]	14	9	2
Thailand[24,26,45,53-55,88]	7	3	
USA[10,18,28,32,48,61,69]	7	2	1
Spain [36,40,58,62,70,91,93]	7	4	2
Taiwan [12,39,64,71,82,84,96]	7	5	2
China [60,73,74,76,86]	5	4	
Israel [23,47,92,93]	4	3	
Germany [10,40,43,63]	4	3	
Italy [25,33,37]	3	3	
Japan [76,81,86]	3	3	
Tanzania [19,66,75]	3	3	
India [49,50,80]	3	1	1
Canada [65,67,85]	3	2	
UK [22,30,89]	3	3	
France [68,79]	2	1	1
South Africa [13,81]	2	1	
Brazil [21,34]	2	2	
Greece [90]	1	1	
Hungary [95]	1	1	
Lebanon [27]	1	-	
Malaysia [29]	1	-	1
Mexico [72]	1	1	
Saudi Arabia [20]	1	1	
Turkey [78]	1	1	
Continent			
Asia [12-14,16,17,20,23,24,25,27,29,31,35,38,39,42,44-47,49, 55,57,59,60,64,71,73,74,76,80-82 ,84,86-88,92,93,96]	46	29	6
Europe [11,22,25,30,33,35,37,40,41,43,58,62,63,68,70,78,79,89-91,94,95]	22	17	3
North America [10,18,28,32,48,61,65,67,69,85]	10	4	1
Africa [15,19,66,75,83]	5	4	-
South America [21,34,72]	3	3	-
More than 1 continent [56]	1	-	-

Income group			
High-income countries [10-14,16-18,20,22,23,25,28,30-33,35-44,46-48,51,52,57-59,61-65,67-71,76,79,81,82,84-86,89-96,]	60	41	8
Low- and middle-income countries [15,19,21,23,25,27,29,34,45,50,53-55,60,66,72-75,77,78,80,83,87,88]	26	16	2
High-income countries AND Low- and middle-income countries [56]	1	-	-
Study design			
Case cohort study [10,12,24-28,31,40,44,46,55,58,61,63-65,67-69,85-87]	24	14	
Retrospective cohort study [11,13-17,20,21,23,29,33-38,41-43,45,47,48,50-54,59,60,71,73,74,76-78,81-84,88,89,93,95,96]	44	32	
Prospective cohort study [18,19,30,32,39,49,56,62,66,70,72,75,79,80,90-92,94]	18	11	
Year group			
1991-1999[10,60,15,16,17,62,21,25,28,36,46,93,94]	13	10	-
2000-2009 [11-14,18-20,22-24,26,27,29-35,37-45,47,49-52,54,55,57,58,61,63,64,67-69,89-92,95,96]	49	31	6
2010-2018 [48,53,54,59,65,66,70-88]	25	16	4
Pathogen			
Escherichia coli [11,24,30,33,35-37,40,43,45,52,55,58,59,68,70,71,73,76,86,87,91,94]	23	16	3
Klebsiella pneumoniae [15,16,20,21,25,29,32,34,41,43,47,61,62,74,78,83,95,96]	17	11	1
E. coli and *K. pneumoniae* [10,13,14,17,26,28,38,43,44,46,48,50,51,54,57,60,63,69,85,88,89]	20	13	2
Gram-negative bacteria [12,18,19,22,23,27,31,39,42,49,53,56,64-67,72,75,77,79-82,84,90,92,93]	27	17	4
Study setting			
Entire hospital[1011,16,18,20-27,29,30,33-38,40-46,48-50,52-55,58-60,62,65-69,73,74,76,82,85,86,90-96]	57	40	7
Intensive care unit [32,61,64,75,79-81,88,89]	9	5	1
Pediatric ward [17,19,28,51,57,78,83,88]	8	7	-
Neonatal ward [15,61,64,71,75]	5	3	-
Neonatal intensive care unit [61,64,75]	3	2	-
Medical ward [13,39,70]	3	-	2
Not provided [31,47]	2	-	-
Emergency Department [12,84]	2	2	-
Surgical ward [32,56]	2	-	-
Burn unit [32]	1	-	-
Oncology [72]	1	1	-
Referral centre for hepatopacreaticobiliary diseases [77]	1	-	-
Hematological [14]	1	1	-

Study population			
All kinds of patients[10-13,14,18,20-27,29,30,34,35,39-41,43-46,48-50,52-56,58,60,62,63,65-69,76,82,84-86,90,92-95]	55	36	7
Intensive care unit patients [32,79-81,87,89]	6	3	1
Children [17,19,28,51,57,78,83,88]	8	7	-
Neonates [15,61,64,71,75]	5	3	-
Cancer patients [33,51,59,72,91]	5	5	-
Immunocompromised patients [51]	1	1	-
Diabetic patients [96]	1	1	-
Elderly patients [70]	1	-	1
Patients with chemotherapy/stem cell transplantation [14,91]	2	2	-
Patients after prostatitis biopsy [42]	1	-	1
Lungs transplantation patients [47]	1	-	-
Hematological patients [73]	1	1	-
All except cardiothoracic therapy, transplant surgery, burns [74]	1	1	
Patients with pyogenic liver abscess [77]	1	-	-
Data reported			
Treatment information [10,12-13,23-25,30-38,40,44-49,51,52,54-65,67,68,70-96]	74	50	6
Appropriateness of treatment[10,12-14,16,17,19-21,23-26,30-38,40,44-46,48,49,51,52,54-56,58-60,62-65,67,68,70,72-74,76,77,79,81,83-86,89-96]	62	45	5
Empirical therapy [14,16,17,24,25,33,35-38,40,44,51,52,56,58,59,63,76,81,83,94]	22	16	2
Treatment outcome [10,12-21,25,26,30-38,40,44-49,51,52,54-57,59-65,67,68,72-74,76,78-81,83-86,88-92,94-96]	64	45	3
Minimum inhibitory concentration results [10,11,13,14,16-19,22-25,27,28,32,33,35-41,43,44,47,50-52,54-59,62,63,66,68,69,76-78,80,81,83,85-87,89,94,95]	52	34	4
AmpC genotyping [10,11,17,32,41,46,50,56,57,65,66,70,86]	13	6	2

Supplementary table S4: Characteristics for each study

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Lautenbach E[10]	1997-1998	USA	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality; LOS	Risk factors for infection with ESBL-producing pathogens, difference in clinical outcomes of infections: resistant vs. susceptible organisms	EC, KP
Kim SH[14]	2007-2008	South Korea	Cohort study, Retrospective	Non-ESBL-infection	Patients who received either chemotherapy or stem cell transplantation; neutropenic fever	Hematological ward, Others	All-cause mortality (28 day)	Risk factors for acquisition of ESBL, appropriateness of empirical antimicrobial therapy, clinical outcomes in relation to ESBL production	EC, KP
Chayakulkeere M[53]	2015-2015	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Prevalence & risk factors for infections with & antibiotic susceptibility patterns of & outcomes of patients infected with ESBL-producing-GNB	GNB
Apisarnthanarak A[54]	2003-2007	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Predictors for mortality associated with community-onset BSI with ESBL-producing pathogens, initial empirical antimicrobial regimens, associated hospital resource utilisation,costs accrued after diagnosis of BSI	EC, KP
Apisarnthanarak A[55]	2003-2004	Thailand	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Mortality associated with community-onset infection due to ESBL-producing pathogens, associated hospital resource use, post-infection hospital cost	EC
Jean SS[56]	2010-2011	Portugal, Columbia, the Philippines, Taiwan, Thailand	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Surgical ward	Attributable mortality, LOS	Clinical impact on hospitalised patients with community-acquired complicated intra-abdominal infection: ESBL-producing- vs. non-ESBL-producing pathogens	GNB
Lee J[57]	1999-2005	South Korea	interventional studies	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	impact of a change in antibiotic policy on ESBL-prevalence	EC, KP
Briongos-Figuero L.S[58]	2009-2010	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Characteristics &associated risk factors for EBSL-enterobacteria-UTIs	EC
Ha YE[59]	2010-2012	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with cancer	Entire hospital	All-cause mortality (28 day)	Clinical &molecular epidemiology of ESBL-EC bacteraemia, clinical impact of ESBLs on patient outcome	EC
Du B[60]	1997-1999	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for nosocomial ESBL-EC- and ESBL-KP- bacteraemia & influence on patient outcome.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Stone PW[61]	2001	USA	Case cohort study	Non-ESBL-infection	Neonates at NICU	NICU	LOS	costs of interventions aimed at controlling the outbreak, attributable length of stay associated with infection and colonisation with ESBL-KP	KP
Pillay T[15]	1995-1996	South Africa	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Use of piperacillin/tazobactam in treatment of KP- infection	KP
Kim BN[16]	1999-2000	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, LOS	Prevalence & clinical characteristics of ESBL-KP- bacteraemia, impact of ESBL- production on outcome of patients with KP-bacteraemia in endemic situation.	KP
Kim YK[17]	1993-1998	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Risk factors & clinical outcomes & clinical responses to treatment of ESBL-EC- and ESBL-KP-bacteraemia, prevalence and types of their ESBLs	EC, KP
Bhavnani SM[18]	2001-2002	USA	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Risk factors for occurrence of invasive ESBL-EC- and ESBL-KP-infections, factors associated with clinical outcome, drug regimens for treatment of infections associated ESBL/non-ESBL strains in real-life clinical practice, clinical response rates for patients treated with cephalosporins/other classes of antimicrobial agents, /carbapenems, clinical response for those patients with infection associated with ESBL and non–ESBL-producing strains with MIC values V8 Ag/mL treated with cephalosporins.	GNB
Blomberg B[19]	2001-2002	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates, children	Pediatric ward	All-cause mortality	Prevalence & clinical implications of ESBL production in EC-,KP-, Salmonellae- septicemia	GNB
Pena C[62]	1993-1995	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Clinical epidemiology& outcome of ESBL-KP- bacteraemia, relevance of ESBL strains in mortality of patients with hospital-acquired KP-BSI.	KP
Kola A[63]	2002-2004	Germany	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Outcomes of ESBL-EC- and ESBL-KP-infections	EC, KP
Tsai MH[64]	2001-2012	Taiwan	Case cohort study	Control group: non-ESBL-infection, second control group: all hospitalised patients	Neonates at NICU	NICU	Attributable mortality, all-cause mortality, LOS	Clinical features& risk factors& molecular epidemiology of ESBL-GNB	GNB
Maslikowska JA[65]	2010-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	Differences in clinical & microbiological outcome, mortality, and/or hospital resource use: ESBL-EC- and ESBL-Ks- vs non-ESBL-EC- and non-ESBL-Ks-infections	GNB

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Onken A[66]	2012-2013	Tanzania	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Most common bacterial pathogens causing BSI, antimicrobial susceptibility	GNB
Nguyen ML[67]	2005-2010	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Risk factors for & patient outcomes associated with ESBL-EC- and ESBL-Ks- bacteraemia, appropriateness of empiric antibiotic therapy & effect of inappropriate empiric therapy on outcomes	GNB
Denis B[68]	2005-2009	France	Case-control study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Prevalence & risk factors for ESBL-EC bacteraemia, impact on length of stay &30day mortality	EC
Chopra T[69]	2004-2009	USA	Case cohort study	Case 2(Control1): non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Predictors of ESBL-EC- and ESBL-KP-BSI, focus on cefepime exposure.	EC, KP
Panhotra BR[20]	2001-2003	Kingdom of Saudi Arabia	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors & clinical outcome of ESBL-KP-bacteraemia (hospital acquired)	KP
Marra AR[21]	1996-2001	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	ESBL-KP- associated mortality	KP
Skippen I[22]	2003-2005	UK	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-invasive transmission of organism in the healthcare setting	GNB
Schwaber MJ[23]	2000-2003	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Outcomes of ESBL-production in Enterobacteriaceae-bacteraemia.	GNB
Apisarnthanarak A[24]	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All adult patients	Entire hospital	All-cause mortality, LOS	Clinical & molecular epidemiologic factors associated with community onset ESBL-EC- infections, hospital resource utilisation, estimate costs associated with medical care (hospitalised patients)	EC
Tumbarello M[25]	1999-2003	Italy	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS, ICU-LOS	Factors associated with isolation of ESBL- KP-strains	KP
Zeistner R[11]	2008-2010	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital,	All-cause mortality, LOS	Difference in mortality: ESBL-EC-BSIs vs. non-ESBL-EC-BSIs, molecular epidemiology of ESBL-positive isolates	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Apisarnthanarak A[26]	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-infections (healthcare associated)	EC, KP
Kanafani ZA[27]	2003	Lebanon	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Epidemiology of infections with ESBL-EC and ESBL-Ks at AUBMC risk factors & outcomes of infections - focus on effect of prior antibiotic administration & the risks imparted by specific classes of antimicrobial agents	GNB
Zaoutis TE[28]	1999-2003	USA	Case cohort study	Non-ESBL-infection	Children	Entire hospital	All-cause mortality, LOS	Risk factors & outcomes associated with ESBL-EC-and ESBL-KP-BSI	EC, KP
Loh LC[29]	2003-2004	Malaysia	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Impact of ESBL-KP-respiratory tract infections on hospital mortality, requirement for mechanical ventilation & length stay	KP
Melzer M[30]	2003-2005	UK	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Differences in mortality & length of hospital stay &time from bacteraemia to death in patients with ESBL-EC- vs. non-ESBL-EC-bacteremic-infection	EC
Song KH[31]	2000-2006	South Korea	Case cohort study	Non-ESBL-infection	Patients with spontaneous bacterial peritonitis	Not provided	All-cause mortality (28 day)	Outcomes of ESBL-EC-and ESBL-Ks- vs non-ESBL-EC-and ESBL-Ks-SBP (based on isolation from ascites), impact of ineffective initial antimicrobial therapy on outcome in patients with ESBL-EC- and ESBL-Ks-SBP, risk factors for infection by ESBL-producing microorganisms.	GNB
Bennett JW[32]	2004-2008	USA	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU, Surgical ward, Burn unit	All-cause mortality (28 day)	ESBL types and strain variability, presence of host factors to determine potential role in morbidity and mortality during ESBL-KP-infections	KP
Trecarichi EM[33]	2000-2007	Italy	Cohort study, retrospective	Non-ESBL-infection	Patients with hematological malignancies	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality in patients suffering from hematological malignancies with concurrent EC-bacteraemia. Focus on impact of ESBL- production & fluoroquinolone resistance by bacterial isolates	EC
Tuon FF[34]	2006-2009	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Risk factors & mortality rate in ESBL-KP-bacteraemia	KP
Kang CI[35]	2008-2009	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors of ESBL-EC among community-onset bacteraemia, treatment outcomes	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Pena C[36]	1996-2003	Spain	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality among patients with EC- infections	EC
Tumbarello M[37]	2006	Italy	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	ICU, Medical ward, Entire hospital, surgical wide	All-cause mortality (21 day), LOS	Clinical &economic impacts of ESBL production, inadequate Initial Antibiotic Therapy of EC-BSI	EC
Kang CI[38]	2006-2009	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality (28 day)	Impact of ESBL-producing bacteraemia on outcome in patients with hematologic malignancy.	EC, KP
Wu YH[39]	2009-2012	Taiwan	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Medical ward	LOS	Host-related risk factors for community-onset UTI due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production, clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens	GNB
Rodriguez-Bano J[40]	2004-2006	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Epidemiology& risk factors (focus on previous antimicrobial use) & mortality rate for patients with ESBL-EC-COBSI	EC
Gürtnke S[41]	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Distribution of ESBL genotypes, hospital mortality in cases of ESBL-KP-BSI	KP
Oh MM[42]	2006-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients after Prostatitis Biopsy	Entire hospital	LOS	Impact of ESBL-positive-strains on clinical course & progression to chronic prostatitis in patients with postbiopsy acute prostatitis.	GNB
Leistner R[43]	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Financial disease burden attributable to ESBL-positive species in cases of EC-and KP-BSI	EC, KP
Lin JN[12]	2005-2009	Taiwan	Case cohort study	Non-ESBL-infection	All kinds of patients	Emergency Room	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Clinical & microbiological characteristics, risk factors for acquisition of infection, prescription of initial empirical antibiotics mortality rate of infection	GNB
Su NS[44]	2006-2010	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Clinical usefulness of breakpoints for treatment of Enterobacteriaceae-bacteraemia, (focus on EC- and Ks-bacteraemia): CLSI 2009- vs. CLSI 2010-guidelines.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Anunnatsiri S[45]	2005-2006	Thailand	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Incidence of ESBL-EC-septicemia, factors associated with infection & clinical outcomes	EC
Kang CI[46]	1998-2002	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Hospital-wide	All-cause mortality (28 day)	Risk factors for mortality & treatment outcome of ESBL-EC- and ESBL-KP-BSI	EC, KP
Raviv Y[47]	2004-2007	Israel	Cohort study, retrospective	Control group: non-ESBL-infection, second control group: no infection	patients with lung transplantation	Not provided	All-cause mortality (28 day)	Outcomes of lung transplant recipients infected by CRKP and ESBL carbapenem-sensitive KP (referred to MDR-KP)	KP
Kim HJ[13]	2005-2010	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Medical ward	All-cause mortality (28 day), LOS	Clinical outcome of patients with biliary tract infection: ESBL-producing bacterial isolates vs. non-ESBL-producing-bacterial isolates, predictors of poor prognosis, impact of ineffective antimicrobial therapy on clinical outcome	EC, KP
MacVane SH[48]	2011-2012	USA	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	clinical & economic outcomes of patients with ESBL-EC- and ESBL-KP-UTI vs. non-ESBL-EC- and non-ESBL-KP-UTI	EC, KP
Abhilash KP[49]	2007	India	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Prevalence & risk factors & outcome of antibiotic treatment among hospitalised patients with ESBL-EC- and ESBL-Ks-BSI	GNB
Shanthi M[50]	2006	India	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Prevalence & impact on clinical outcome of ESBL-production among nosocomial isolates of EC & KP	EC, KP
Han SB[51]	2009-2013	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children (immunocompromised, with cancer, neutropenic fever)	Pediatric ward	Attributable mortality, all-cause mortality (28 day)	Clinical outcomes of ESBL-EC- and ESBL-KP-bacteraemia & their antibiotic susceptibilities	EC, KP
Lee S[52]	2009-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with Acute Pyelonephritis	Entire hospital	All-cause mortality (14 day), LOS	Impact of ESBL on clinical outcomes of Acute Pyelonephritis treated with empirical ceftriaxone (which was inappropriate for ESBL-producing organisms)	EC
Artero A[70]	2013-2015	Spain	Cohort study, prospective	Non-ESBL-infection	Elderly	Medical ward	All-cause mortality, LOS	Identify clinical factors to predict ESBL-EC among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-EC	EC

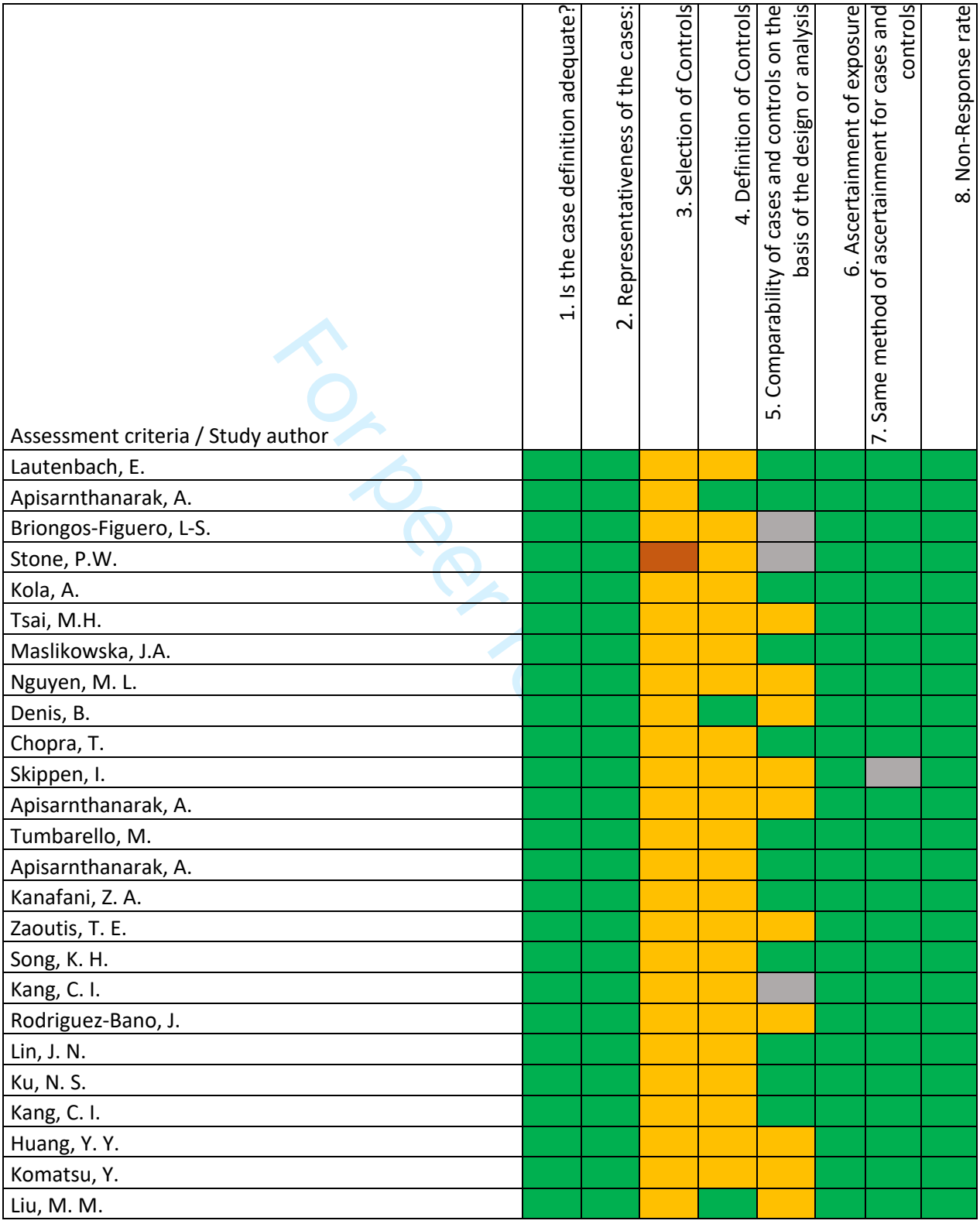
	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Chen IL[71]	2004-2015	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Compare the clinical characteristics & laboratory data of preterm babies with EC BSI: survival vs. nonsurvival groups, ESBL vs non-ESBL groups, determine the predictive factors of EC BSI in preterm babies	EC
Islas-Munoz B[72]	2016-2017	Mexico	Cohort study, prospective	Non-ESBL-infection	Cancer patients	Oncological ward	All-cause mortality (28 day)	Evaluate the clinical epidemiological characteristics & risk factors associated with mortality in cancer patients with BSI-special emphasis on MDR bacteria	GNB (and others)
Ma J[73]	2012-2015		Cohort study, retrospective	Non-ESBL-infection	Patients with hematological diseases	Entire hospital	All-cause mortality (28 day)	Evaluate the antimicrobial resistance & clinical features & risk factors for septic shock & death of nosocomial EC-BSI	EC
Man MY[74]	2009-2016	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients, except patients from Burn unit, transplant surgery ward or with thoracic therapy	Entire hospital	All-cause mortality (28 day)	Evaluate the incidence & clinical characteristics & outcomes of patients with KP BSI in critical care & general ward settings	KP
Marando R[75]	2016	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates	NICU	All-cause mortality	Investigate factors associated with ESBL-PE neonatal sepsis & mortality among neonates, characterise selected isolates to show virulence potential & transmission dynamics	GNB
Namikawa H[76]	2011-2015	Japan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate clinical characteristics of patients with ESBL-EC-BSI	EC
Shi SH[77]	2008-2015	China	Cohort study, retrospective	Non-ESBL-infection	Patients with pyogenic liver abscess	Centre for hepatopancreaticobiliary diseases	All-cause mortality, LOS	Aetiology & morbidity & clinical characteristics of pyogenic liver abscess caused by ESBL-PE	GN
Tanir Basaranoglu S[78]	2011-2015	Turkey	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	Assess risk factors for health care associated ESBL-KP-BSI in children, analyze clinical outcomes: ESBL-KP vs. non-ESBL-KP	KP
Razazi K[79]	2009-2015	France	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality, LOS, ICU-LOS	Determine, among ESBL-PE carriers, the prevalence & associated factors & clinical impact of ESBL-PE pneumonia, determine factors associated with ICUAP caused by carbapenem-resistant bacteria	GNB

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Ray S[80]	2014-2016	India	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Investigate spectrum of microbial resistance pattern in the community and their effects on mortality	GNB
Haruki Y[81]	2006-2016	Japan	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Compare the clinical characteristics & outcomes of critically ill patients in an ICU, who were hospitalised for BSI caused by ESBL-EC or non-ESBL-EC.	GNB
Lin WT[82]	2009-2014	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate the clinical manifestations & bacteriological features of culture-proven, GNB arthritis	GNB
Buys H[83]	2006-2011	South Africa	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Describe the clinical presentation of KPBSI, risk factors associated with ESBL-KPBSI, antibiotic susceptibility patterns of the KP isolates & KPBSI mortality including factors associated with in-patient mortality	KP
Lee CC[84]	2008-2013	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Emergency Department	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Analyse the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics & bacteraemia severity by using a propensity-matched analysis (PSM)	GNB
Huang YY[85]	2011-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Determine cumulative incidence of ESBL urosepsis, identify major risk factors for ESBL urosepsis, determine impact of international travel on development of ESBL urosepsis	EC, KP
Komatsu Y[86]	2008-2013	Japan	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Identify risk factors & clinical outcomes in patients with BSI due to ESBL- or carbapenemase-producing EC, determine prevalence & genetic background	EC
Liu MM[87]	2011-2016	China	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	ICU-patients	ICU	All-cause mortality	Identify risk factors for ESBL-producing ECBSI among carriers at ICU	EC
Nivesvivat T[88]	2010-2017	Thailand	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality, LOS	Determine prevalence, risk factors & clinical outcomes of ESBL-producing EB in paediatric BSI	EC, KP

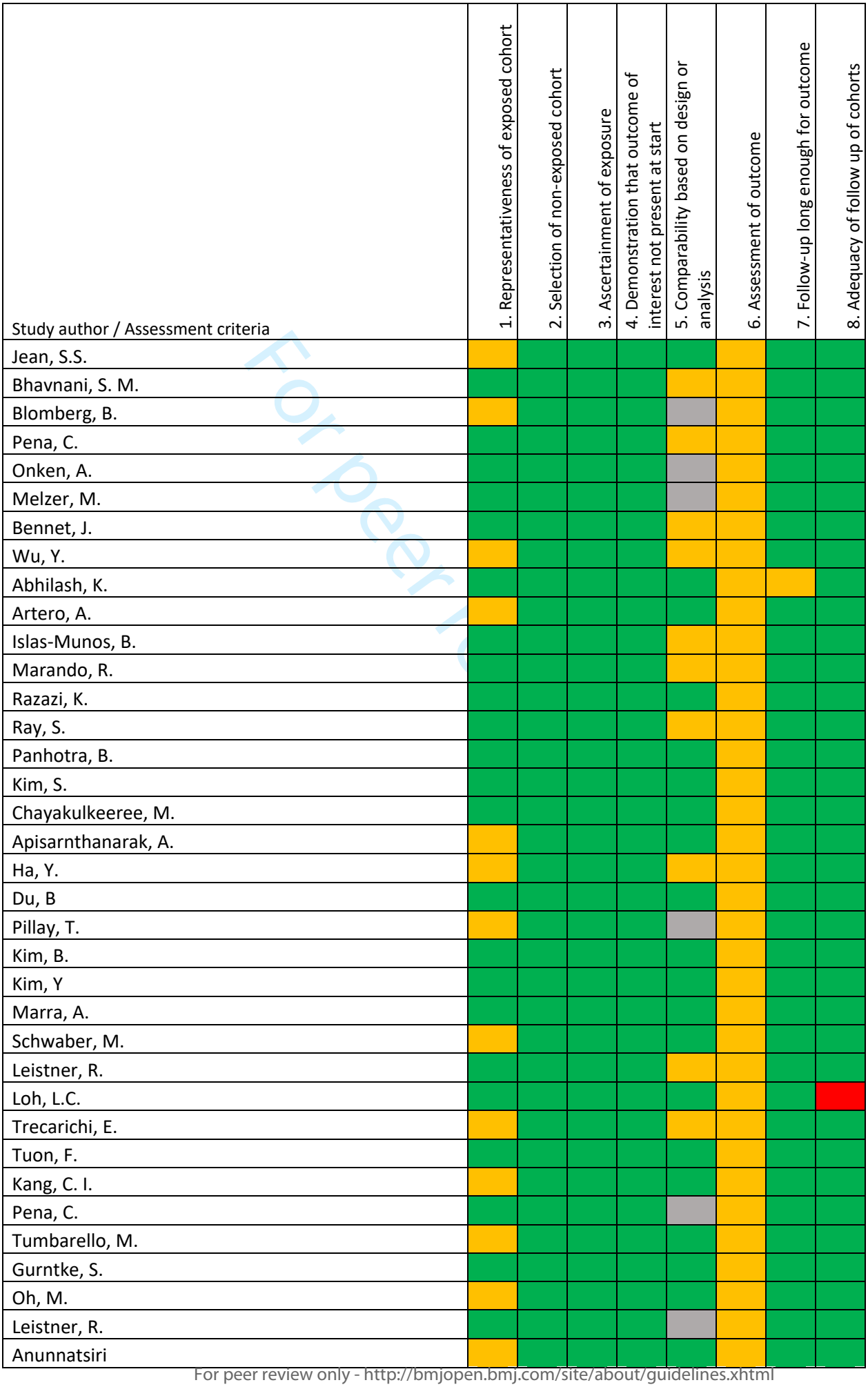
	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Cordery RJ[89]	2004-2006	UK	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Elucidate specific risk factors for the acquisition of ESBL infection in the ICU; all-cause mortality (in ICU) compared in patients with infections due to ESBL- and non-ESBL-producing organisms	GNB
Paikos GL[90]	2003-2005	Greece	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Identify risk factors associated BSI caused by integron-carrying EB; evaluate the consequences of these genetic elements on patient outcome	GNB
Gudiol C[91]	2006-2008	Spain	Cohort study, prospective	Non-ESBL-infection	Cancer patients and hematopoietic stem cell transplant patients	Entire hospital	All-cause mortality	Assess clinical features, risk factors, molecular epidemiology & outcome of ESBLEC BSI in hospitalised cancer patients	EC
Marchaim D[92]	2006-2008	Israel	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Define predictors & outcomes of ESBL BSI among patients with bacteraemia due to EB upon hospital admission	GNB
Menashe G[93]	1997	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Determine: prevalence of ESBL-P organisms among adult patients with nosocomial EB BSI treated in our institution; association between ESBL production & resistance to other antibiotics; clinical characteristics of patients with nosocomial ESBL-P BSI compared with those infected with non-producing strains; impact of ESBL production on outcome of patients with nosocomial EB BSI	GNB
Ortega M[94]	1991-2007	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Describe source, resistance rate to fluoroquinolone & beta-lactam antibiotics and mortality of EC BSI episodes in a single institution; identify predictive factors for isolation of fluoroquinolone-resistant or ESBL- producing strains.	EC
Szilgyi M[95]	2005-2008	Hungary	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality,	Investigate risk factors for & outcomes of BSI caused by ESBL-producing and ESBL-non-producing KP	KP
Tsai SS[96]	2005-2006	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Diabetic patients	Entire hospital	All-cause mortality	Analyze characteristics, risk factors & outcomes of diabetic patients with community- vs. hospital-acquired KP BSI	KP

EC = *Escherichia coli*
KP = *Klebsiella pneumoniae*
GNB = Gram-negative bacteria
BSI = Bloodstream infection
UTI = Urinary tract infection
ICU = Intensive care unit
NICU = Neonatal intensive care unit
ESBL-PE = Extended-spectrum beta-lactamase-producing Enterobacteriaceae
EB = Enterobacteriaceae
LOS = Length of stay

Supplementary table S5: Risk of bias assessment of case cohort studies according to Newcastle - Ottawa quality assessment scale:



Risk of bias assessment of cohort studies according to Newcastle - Ottawa quality assessment scale:



Raviv, Y.								
Kim, H.J.								
MacVane, S.								
Shanthi								
Han, S.B.								
Lee, S.								
Chen, I-L.								
Ma, J.								
Man, M.								
Namikawa, H.								
Shi, S.								
Tanir Basarangolu, S.								
Haruki, Y.								
Lin, W.								
Buys, H.								
Lee, C.C.								
Nivesvivat, T.								

Supplementary table S6: Source of heterogeneity among effect estimates in studies on ESBL bloodstream infections in comparison with patients with non-ESBL bloodstream infections assessed using univariate meta-regression:

Subgroups / Outcome	All-cause mortality	Length of Stay
Mortality time	0.85	-
Pathogen	0.45	0.34
Study design	0.51	0.21
Study country	0.22	0.09
Income classification	0.17	0.80
Study period	0.57	0.78
Study setting: ICU ward	0.78	0.97
Study setting: Neonatal ward	0.62	0.97
Study setting: Pediatric ward	0.96	0.96
Study population: ICU patients	1.00	-
Study population: Children	0.96	0.96
Study population: Neonates	0.62	0.97
Information about therapy	0.53	
Appropriatness of therapy reported	0.68	
Information about outcome of therapy	0.74	-
MIC reported	0.28	-

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	suppl.material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 and suppl. material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	suppl.material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 and suppl. material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030266.R3
Article Type:	Original research
Date Submitted by the Author:	10-Dec-2019
Complete List of Authors:	Shamsrizi, Parichehr; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Gladstone, Beryl Primrose ; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Carrara, Elena; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Luise, Dora; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Cona, Andrea; ASST Santi Paolo e Carlo, Clinic of Infectious and Tropical Diseases, Department of Health Sciences Bovo, Chiara; Integrated University Hospital of Verona, Medical Direction Tacconelli, Evelina; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Epidemiology
Keywords:	Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

AUTHORS:

Parichehr Shamsrizi[1], Beryl Primrose Gladstone[1], Elena Carrara[2], Dora Luise[2], Andrea Cona[3], Chiara Bovo[4], Evelina Tacconelli[1,2]

AFFILIATIONS:

1) Division of Infectious Disease, Department of Internal Medicine I, DZIF Partner site, Tübingen University Hospital, Tübingen, Germany
2) Division of Infectious Disease, Department of Diagnostic and Public Health, University Hospital of Verona, Verona, Italy
3) Clinic of Infectious and Tropical Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy.
4) Medical Direction, University Hospital of Verona, Verona, Italy

CORRESPONDING AUTHOR: Elena Carrara, MD

Address: Division of Infectious Disease, Department of Diagnostic and Public Health, University Hospital of Verona, Verona, Italy

Piazzale L.A. Scuro 10, Dipartimento di Malattie Infettive, Policlinico Borgo Roma, 37100 Verona, Italy.

Phone number: +39 3339566252

Email: elena.carrara@univr.it

WORD COUNT: 2921

ABSTRACT

Objective To assess the variation of effect estimates in the analysis of mortality and length of stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*.

Design Systematic review and meta-analysis

Methods Literature search for clinical studies from 1 January 1960 to 1 October 2018 was conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream infections (BSIs) and non-invasive infections. Any change in the effect estimates was assessed by grouping studies according to design, setting, economy-based country classification, reporting period, microbiological aetiology, infection type, and adjustment for appropriateness of empirical treatment. The impact of ESBL production was calculated using random effect meta-analysis and heterogeneity was evaluated by I^2 statistics and metaregression.

Results Eighty-four studies including 22,030 patients and 149 outcome measures were included in the meta-analysis. Most studies were retrospective cohorts from high-income countries, providing unadjusted estimates. ESBL production in patients with BSIs (56 studies) increased the RR for all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; p<0.001), attributable mortality (16 studies) by 1.75 (95% CI: 1.448-2.108; p<0.001), and WMD in the intensive care unit by 3.07 days (95% CI: 1.61-4.54; p<0.001). WMD in hospital LOS was significantly higher in BSIs (4.41 days; 95% CI: 3.37-5.46; p<0.001) and non-invasive (2.19 days; 95% CI: 1.56-2.81; p<0.001). Subgroup analyses showed variation of estimates by study design, population, strain, and assessment of appropriateness of empiric treatment. High heterogeneity was observed in all analyses.

Conclusions Current evidence of the clinical burden of infections caused by ESBL-producing bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from retrospective studies. Despite these limitations, ESBL production in strains causing BSIs seems associated with higher all-cause and attributable mortality and longer hospitalisation.

KEYWORDS

Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Evidence of the impact of ESBL production on mortality and length of stay in strains causing bacteremic and non-bacteremic infections was collected systematically.
- Effect of multiple epidemiological and clinical variables was assessed in the calculation of estimates.
- Heterogeneity among studies was assessed.
- Only few studies had been performed in high-risk populations or low-income countries.

INTRODUCTION

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* are responsible for high morbidity and mortality worldwide.[1,2,3] The 2018 World Health Organization list of antibiotic-resistant pathogens identified mortality as the most important criteria to prioritise bacteria for research and development of new, effective antibiotics.[1] In this prioritisation exercise, ESBL-producing *Enterobacteriaceae* were designated a critical priority because of their high all-cause mortality and high prevalence globally in healthcare-associated and community-acquired infections. The incidence and attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing *Enterobacteriaceae*, in European countries has been recently estimated using a modelling analysis.[4] In 2015 ESBL-producing *Escherichia coli* was responsible for almost 300,000 infections in Europe and 9,000 attributable deaths, and ESBL-producing *Klebsiella pneumoniae* caused around 70,000 infections and more than 3,500 deaths. The major limitation of this analysis is the sparseness of evidence on mortality due to ESBL-producing bacteria, which was limited largely to studies conducted in high-income countries.

Two systematic reviews have been performed to define the impact of ESBL production on mortality due to *Enterobacteriaceae*.[2,3] Both meta-analyses included studies targeting bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated bacteraemia compared to non-ESBL *Enterobacteriaceae* bacteraemia. A major drawback of the analyses, highlighted by the authors, was the lack of control for confounding and limited adjustment for empiric therapy. No systematic review has been performed to assess attributable mortality and other indicators of clinical impact such as length of stay (LOS).

Because estimates of clinical burden drive policy design for antibiotic stewardship and infection control interventions, precise and current estimates are essential. The objective of this systematic review and meta-analysis was to assess the variation of effect estimates in the analysis of mortality and LOS in patients with infections due to ESBL-producing *Enterobacteriaceae*.

METHODS

Literature search strategy

The search was performed by 2 researchers (BPG and PS) in PubMed on 05 October 2018 using search terms (supplementary table S1) relevant to the following combinations: (ESBL AND Escherichia coli AND mortality) OR (ESBL AND Klebsiella pneumoniae AND

mortality) OR (ESBL AND Escherichia coli AND length of stay OR length of hospitalisation) OR (ESBL AND Klebsiella pneumoniae AND length of stay OR length of hospitalisation). Reference lists of retrieved articles were also searched.

Eligibility criteria

We included all clinical studies with a comparison group assessing all-cause mortality, attributable mortality, and overall LOS and intensive care unit stay (ICU) LOS in hospitalised patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018 irrespective of the clinical setting and study design were included. No language restriction has been applied. Diagnostic studies, reviews, case reports, non-clinical studies, and abstracts of conference presentations were not included.

Data extraction

Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted data. In case of disagreement, a third reviewer (DL) was consulted. Extracted data were collected in an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of publication, year of study, time of data collection, study design, comparison group, study setting, population, aetiology, type and site of infection, and raw data related to mortality and LOS/ICU-LOS. Countries were classified as high-, middle-, or low-income using the World Bank Atlas method.[5] Adjusted effect estimates such as odds ratios (ORs) or hazard ratios and quality indicators such as reporting of antibiotic therapy, appropriateness of empirical treatment, resistance mechanisms, and minimum inhibitory concentrations (MICs) were also extracted.

Mortality data were extracted as all-cause mortality or attributable mortality as defined in the studies. Where available, prespecified time periods for mortality assessment (i.e., 14 days, 28 days, in-hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean and standard deviation or median and interquartile range.

Data analysis

The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in patients with ESBL infections compared with those in patients with non-ESBL infections and, where available, with uninfected patients. The impact of ESBL production on attributable and all-cause mortality was calculated with random effect meta-analysis and expressed as RR with

95% confidence interval (CI). WMD in days with 95% CI was calculated to express the excess in LOS and ICU-LOS.

Variation of the effect estimate was assessed by grouping the studies according to the following study/outcome characteristics: mortality time assessment (7 vs 14 days), aetiology (*E. coli* vs *K. pneumoniae*), infection localisation, clinical setting (paediatric, oncology, ICU), economic country areas (high-income countries [HICs] vs low- and medium-income countries [LMICs]), study design, assessment of empiric therapy, and year. Studies were classified according to the type of infections evaluated. Studies on BSIs were defined as those in which patients had positive blood cultures and were admitted to the hospitals with signs and symptoms of systemic inflammatory response and requiring therapy, similarly to the definition adopted by the most recent cohort studies on ESBL infections.[6] Non-invasive infections included non-bacteremic patients with only localised signs and symptoms of infection (such as urinary tract infections or superficial surgical site infections).

Subgroup analysis was computed only if more than 2 studies were available for each group. Heterogeneity was evaluated by using I^2 statistics and metaregression. Overall significance testing was carried out using Wald tests adjusted using the Bonferroni correction. The unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment. Reporting and publication bias was presented in funnel plots (supplementary figure 1 and 2) and tested by Egger's test. Statistical analyses were performed using Stata version 15. Risk of bias was assessed independently by two authors (PS, DL) using the Newcastle - Ottawa quality assessment scale for cohort studies.[7] Studies were classified as low, moderate, or high quality according to AHRQ standards (supplementary table S2). All meta-analyses were performed in accordance with the Cochrane Collaboration recommendations[8] and reported according to the PRISMA statement.[9]

The protocol is available online.

(https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf)

Patient and Public Involvement

There was no patient or public involvement in this systematic review of published literature.

RESULTS

Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an

evidence base of 87 studies (Figure 1).[10-96] The 87 studies included in the qualitative analysis were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies), Thailand (7), USA (7), Taiwan (7), and Spain (7). Sixty (68.9%) studies were performed in HICs, 26 (29.9%) in LMICs, and 1 included both HICs and LMICs.[56] About half (44, 50.6%) were retrospective cohort studies, 24 (27.6%) case cohort studies, and 18 (20.7%) prospective cohort studies; 1 study had an interventional design.[57] The comparison group was patients with infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-infected patients in 2 (2.3%), and both control groups in 3 (3.5%). Most (57, 65.5%) studies included data from the entire hospital, while a few focused on specific settings, mainly ICUs (9, 10.3%) and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were *E. coli* (23, 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is provided in online supplementary table S3.

Because data in 3 studies [22,61,87] were insufficient for quantitative analysis, 84 (96.6%) studies were included in the meta-analysis analysing data from 22,030 patients and 149 outcome measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study characteristics for all studies are provided in online supplementary table S4. 49 (58.3%) studies were of high quality, 23 (27.3%) were of moderate quality, and 12 (14.3%) were of low quality (supplementary table S5).

All-cause mortality

All-cause mortality was reported in 81 studies including 21,942 patients (56 on BSIs and 7 on non-invasive infections). ESBL production in patients with BSIs increased all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; p<0.001; I^2=45.3%; p<0.001) while studies including non-invasive reported a RR of 1.58 (95% CI: 1.23-2.02; p<0.001) (supplementary figure 3). Among the BSI patients, the RR increased over time from 1.56 (95% CI: 1.15-2.11; p=0.004) in 1991-1999 to 1.74 (95% CI: 1.50-2.01; p<0.001) in 2000-2009, and it was stable in 2010-2018 (1.72, 95% CI: 1.39-2.13; p<0.001). The RR was higher in studies assessing appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; p<0.001) than in those that did not (RR=1.55; 95% CI 1.26-1.90; p<0.001). The subgroup analysis by pathogen showed that ESBL production increased the RR in BSIs due to *E. coli* (RR=1.82; 95% CI: 1.50-2.21; p<0.001) compared to those due to *K. pneumoniae* (RR=1.48; 95% CI: 1.17-1.87; p=0.001). Stratification by population age showed a higher RR in paediatric population (RR=2.09; 95% CI: 1.62-2.71; p<0.001). Effect estimates did not vary significantly by study country, mortality time assessment (14 vs 28 days), ESBL molecular resistance mechanisms, or study

design (Figure 2 and online supplementary figure 4). Adjusted estimates for inappropriate empirical antibiotic therapy were provided for 14 studies. The pooled unadjusted OR for all-cause mortality was 2.91 (95% CI: 2.23-3.81; p<0.001, I^2=27.1%; p=0.164) and the pooled OR after adjusting for receipt of appropriate empirical treatment was 3.22 (95% CI: 1.53-6.76; p=0.002; I^2=87.5%; p<0.001). The impact of ESBL production on LOS and mortality varied according to the infection type, with higher effect in intra-abdominal, respiratory and BSIs (supplemental figure 5 and 6).

Attributable mortality

Attributable mortality was analysed in 16 studies including 2,885 patients. All studies were performed in HICs. ESBL production in patients with BSIs increased the risk of attributable mortality by a factor of 1.75 (95% CI: 1.45-2.11; p<0.001; I^2=0%; p<0.001). The RR increased over time from 1.53 (95% CI: 1.10-2.12; p=0.011) in 1991-1999 to 1.91 (95% CI: 1.43-2.54; p<0.001) in 2000-2009 (Figure 3). Pathogen-specific RR for attributable mortality was 1.60 (95% CI: 1.18-2.15; p=0.002) for *K. pneumoniae* and 1.76 (95% CI: 1.33-2.34; p<0.001) when the gram-negative organisms were analysed all together without species differentiation. The subgroup analysis showed the RR was lower in case cohort studies (1.56; 95% CI: 1.09-2.25; p=0.016) than in cohort studies (1.80; 95% CI: 1.37-2.37; p<0.001).

Length of stay

LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive) analysing 38 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95% CI: 3.37-5.46; p<0.001) and decreased from 5.72 days (95% CI: 2.69-8.75; p<0.001) in 1991-1999 to 4.22 days (95% CI: 3.02-5.43; p<0.001) in 2000-2009 and was stable up to 2018 (4.30 days; 95% CI: 1.38-7.22; p=0,004). Higher WMD (p<0.001) was observed for BSIs due to *K. pneumoniae* (7.67 days; 4.63-10.71) than for those due to *E. coli* (6.07 days; 95% CI 3.71-8.43). Retrospective cohort studies reported higher (p<0.001) WMD (6.43 days; 95% CI: 4.66-8.21; p<0.001) than case cohort studies (3.32 days; 95% CI: 2.03-4.61). Studies in HICs showed higher WMD (4.56 days; 95% CI 3.43-5.70; p<0.001) than studies in LMICs (3.55 days; 95% CI 0.84-6.26; p=0.01) (Figure 4).

Studies with non-invasive infections reported a WMD of 2.19 days (95% CI: 1.56-2.81; p<0.001), which decreased from 7.66 (95% CI: 5.83-9.46; p<0.001) in 2000-2009 to 1.44 (95% CI: 0.77-2.10; p<0.001) in 2010-2018 (online supplementary figure 7).

The data on ICU-LOS were provided in 7 studies and showed that BSIs caused by ESBL producers had a WMD of LOS of 3.07 days (95% CI: 1.61-4.54; p<0.001).

Heterogeniety of the studied effect-modifiers did not reach statistical significance when assessed by metaregression (supplementary table S6). Sensitivity analysis based on the quality of studies revealed no notable difference in the effect estimates after exclusion of low-quality studies (data not shown). Egger's test and the funnel plots (online supplementary figure 1 and 2) showed evidence for small study effects (p<0.001) and publication bias.

DISCUSSION

This systematic review shows that ESBL production has a significant impact on the most relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality, attributable mortality, and LOS both in hospital and in ICU were higher for patients with BSIs due to ESBL-producing *Enterobacteriaceae* than for patients with BSIs due to non-ESBL-producing strains. Non-invasive infections caused by ESBL-producing strains were associated with higher all-cause mortality and prolonged LOS. Within the limitation of the low number of studies evaluating specific patient populations, paediatric and cancer patients seemed to suffer a higher impact of ESBL invasive infections than the overall population. Stratifying by pathogen type, the impact of ESBL production was higher for *E. coli* BSIs than for *K. pneumoniae* BSIs. No relevant differences in mortality analysis emerged with stratification by study design or country income level. Impact of ESBL infections on mortality became more evident in more recent studies. Studies reporting on appropriateness of empirical therapy, ESBL resistance mechanisms, and MICs showed a higher clinical impact of ESBL infections than studies not assessing these variables. In particular, pooled ORs adjusted for inappropriate empirical treatment, showed a remarkably higher OR for mortality in patients with ESBL infections.

Our findings confirm the results of previous systematic reviews. Schwaber et al. performed a systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies published through 2003.[2] The authors show a pooled RR for all-cause mortality of 1.85 but, in contrast to our study, they combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in the analysis because of sample size limitations. Rottier et al. analysed studies published through 2010 and adjusting results for inappropriate empirical treatment found an adjusted OR of 1.37.[3] Our study, adding more than 50 studies in 17 years to the Rottier systematic review, confirmed the clinical importance of ESBL production to all-cause mortality and for the first time assessed the role of ESBL production on attributable mortality. We addressed relevant effect-modifiers

through subgroup analyses and found that population, pathogen, and assessment of empiric therapy all had an impact on estimates. Because we believe that appropriate empirical treatment plays a relevant role in invasive infections, we performed a secondary analysis by pooling only adjusted ORs and confirming the significant impact of antibiotic resistance as already shown in a previously published systematic review.[97] The lack of consideration of appropriateness of therapy in the studies evaluating mortality seems to underestimate the impact of ESBL production on mortality. However, studies assessing the impact of appropriate therapy did not provide homogeneous definition and could refer either to empirical or definite therapy or a single component irrespective of the dosage, making results difficult to interpret. Especially in infections with different sources and different clinical severity, the sole contribution of empirical therapy remains challenging to measure. For example, patients with UTI receiving inappropriate empirical antibiotic therapy can potentially show a favourable outcome, most probably due to the high concentration of antibiotic reached in the urinary tract.[98]

Community acquired ESBL infections emerged in the late 1990s and show an increasing trend.[99,100] Recent study shows that community onset ESBL infections are associated with lower mortality compared with healthcare associated and hospital acquired infections.[101] The place of acquisition could not be appropriately addressed in our meta-analysis due to the lack of data in included studies.

Our systematic review contributes to the discussion on the limitation of current evidence for the estimation of mortality due to antibiotic-resistant infections. The impact of ESBL production on LOS in our study has shown that both BSIs and non-invasive infections lead to prolongation of hospitalisation.

Our study has some limitations. Although results of the meta-analyses were significant in all the subgroups, we could analyse only a limited number of studies providing information for subgroups such as haematological patients and low-income countries, making generalizability of results less certain for these specific patient populations. Only a few studies reported MIC data or specific ESBL molecular resistant phenotype (i.e., AmpC). Moreover, publication bias was detected in both the main analyses (all-cause mortality and LOS), thus implying the possibility that results from small studies with non-significant results might have been conducted and not published, resulting in a possible overestimation of our results. The non-homogeneous reporting of some relevant data in published literature (e.g., infection type,

presence of bacteremia, disease severity, underlying comorbidities and resistance mechanism) may also have affected the precision of the estimate. A limited number of patients with non-bacteremic infections was included in our systematic review, thus limiting the generalizability of results to this patients' population. Moreover, patients with ESBL are intrinsically at higher risk of mortality and complications because they are often older, have more comorbidities or higher antibiotic exposure, and are at higher risk of receiving inappropriate empirical treatment.[102] Finally, due to resource constraints, we had to limit our search to PubMed database with the chance of missing relevant studies.

In summary, our systematic review emphasises the importance of suspicion and confirmation of ESBL production as soon as possible for invasive infections and demonstrates that ESBL production increases the risk of attributable mortality and LOS in both hospital and ICU for invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of mortality and prolonged LOS even after adjustment for empiric inappropriate treatment. Control for other relevant effect-modifiers is hindered by the sparseness of published data. Individual patient data (IPD) network meta-analyses are needed to define differences in outcomes between severe intravascular infections and bacteremia. Future studies addressing the clinical burden of drug-resistant infections must include ESBL production and should assess both the impact of molecular mechanisms of resistance and effect on specific patient populations such as haematological patients and those in LMIC.

Acknowledgements We thank Anne McDonough, a professional medical writer who provided medical writing support funded by the authors.

Author Contributions ET contributed to the study concept. BPG and PS performed data analysis. PS and AC extracted data and wrote the first draft of the manuscript. DL contributed to the first draft of the manuscript. EC and ET wrote the final version of the manuscript. CB reviewed the paper. All authors read, edited, and approved the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding This work was supported by the German Center for Infection Research Clinical Research Unit for Health-Care Associated Infections grant number TTU 08.701 and DRIVE-AB (115618). The funder had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Competing interests The authors report no competing interests.

Patient consent Not required

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Requests for data should be addressed to the corresponding author.

REFERENCES

1. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 2018;18:318–27.
2. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:913–20.
3. Rottier WC, Ammerlaan HS, Bonten MJ. Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. *J Antimicrob Chemother* 2012;67:1311–20.
4. Cassini A, Högberg LD, Plachouras D, et al; Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;19:56–66.
5. The World Bank. What is the World Bank Atlas method? https://datahelpdesk.worldbank.org/knowledgebase/articles/77933-what-is-the-world-bank-atlas-method. Accessed January 14, 2019.
6. Rodriguez-Bano J, Gutierrez-Gutierrez B, Machuca I et al. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clin Microbiol Rev 2018; 31. doi:10.1128/CMR.00079-17
7. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M *et al*. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. The Ottawa Health Research Institute: Ottawa, Canada. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed April 14 2015
8. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
9. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
10. Lautenbach E, Patel JB, Bilker WB, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *Clin Infect Dis* 2001;32:1162–71.

11. Leistner R, Sakellariou C, Gurntke S, et al. Mortality and molecular epidemiology associated with extended-spectrum beta-lactamase production in Escherichia coli from bloodstream infection. *Infect Drug Resist* 2014;7:57–62.
12. Lin JN, Chen YH, Chang LL, et al. Clinical characteristics and outcomes of patients with extended-spectrum beta-lactamase-producing bacteremias in the emergency department. *Intern Emerg Med* 2011;6:547–55.
13. Kim HJ, Park JH, Park DI, et al. Clinical impact of extended-spectrum beta-lactamase-producing Enterobacteriaceae in patients with biliary tract infection. *Dig Dis Sci* 2013;58:841–9.
14. Kim SH, Kwon JC, Choi SM, et al. Escherichia coli and Klebsiella pneumoniae bacteremia in patients with neutropenic fever: factors associated with extended-spectrum beta-lactamase production and its impact on outcome. *Ann Hematol* 2013;92:533–41.
15. Pillay T, Pillay DG, Adhikari M, et al. Piperacillin/tazobactam in the treatment of Klebsiella pneumoniae infections in neonates. *Am J Perinatol* 1998;15:47–51.
16. Kim BN, Woo JH, Kim MN, et al. Clinical implications of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae bacteraemia. *J Hosp Infect* 2002;52:99–106.
17. Kim YK, Pai H, Lee HJ, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in children: epidemiology and clinical outcome. *Antimicrob Agents Chemother* 2002;46:1481–91.
18. Bhavnani SM, Ambrose PG, Craig WA, et al. Outcomes evaluation of patients with ESBL- and non-ESBL-producing Escherichia coli and Klebsiella species as defined by CLSI reference methods: report from the SENTRY Antimicrobial Surveillance Program. *Diagn Microbiol Infect Dis* 2006;54:231–6.
19. Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol* 2005;43:745–9.
20. Panhotra BR, Saxena AK, Al-Ghamdi AM. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae hospital acquired bacteremia. Risk factors and clinical outcome. *Saudi Med J* 2004;25:1871–6.
21. Marra AR, Wey SB, Castelo A, et al. Nosocomial bloodstream infections caused by Klebsiella pneumoniae: impact of extended-spectrum beta-lactamase (ESBL) production on clinical outcome in a hospital with high ESBL prevalence. *BMC Infect Dis* 2006;6:24.

22. Skippen I, Shemko M, Turton J, et al. Epidemiology of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp.: a nested case-control study from a tertiary hospital in London. *J Hosp Infect* 2006;64:115–23.
23. Schwaber MJ, Navon-Venezia S, Kaye KS, et al. Clinical and economic impact of bacteremia with extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2006;50:1257–62.
24. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Clinical and molecular epidemiology of community-onset, extended-spectrum beta-lactamase-producing Escherichia coli infections in Thailand: a case-case-control study. *Am J Infect Control* 2007;35:606–12.
25. Tumbarello M, Spanu T, Sanguinetti M, et al. Bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae: risk factors, molecular epidemiology, and clinical outcome. *Antimicrob Agents Chemother* 2006;50:498–504.
26. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Risk factors for and outcomes of healthcare-associated infection due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae in Thailand. *Infect Control Hosp Epidemiol* 2007;28:873–6. doi: 10.1086/518725
27. Kanafani ZA, Mehio-Sibai A, Araj GF, et al. Epidemiology and risk factors for extended-spectrum beta-lactamase-producing organisms: a case control study at a tertiary care center in Lebanon. *Am J Infect Control* 2005;33:326–32.
28. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in children. *Pediatrics* 2005;115:942–9.
29. Loh LC, Nor Izran Hanim Bt Abdul S, Rosdara Masayuni Bt Mohd S, et al. Hospital Outcomes of Adult Respiratory Tract Infections with Extended-Spectrum B-Lactamase (ESBL) Producing Klebsiella Pneumoniae. *Malays J Med Sci* 2007;14:36–40.
30. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing E. coli compared to non-ESBL producing E. coli. *J Infect* 2007;55:254–9. doi: 10.1016/j.jinf.2007.04.007
31. Song KH, Jeon JH, Park WB, et al. Clinical outcomes of spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species: a retrospective matched case-control study. *BMC Infect Dis* 2009;9:41.
32. Bennett JW, Robertson JL, Hospenthal DR, et al. Impact of extended spectrum beta-lactamase producing Klebsiella pneumoniae infections in severely burned patients. *J Am Coll Surg* 2010;211:391–9.

33. Trecarichi EM, Tumbarello M, Spanu T, et al. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by Escherichia coli in patients with hematological malignancies. *J Infect* 2009;58:299–307.
34. Tuon FF, Kruger M, Terreri M, et al. Klebsiella ESBL bacteremia-mortality and risk factors. *Braz J Infect Dis* 2011;15:594–8.
35. Kang CI, Song JH, Chung DR, et al. Risk factors and treatment outcomes of community-onset bacteraemia caused by extended-spectrum beta-lactamase-producing Escherichia coli. *Int J Antimicrob Agents* 2010;36:284–7.
36. Pena C, Gudiol C, Calatayud L, et al. Infections due to Escherichia coli producing extended-spectrum beta-lactamase among hospitalised patients: factors influencing mortality. *J Hosp Infect* 2008;68:116–22.
37. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. *Antimicrob Agents Chemother* 2010;54:4085–91.
38. Kang CI, Chung DR, Ko KS, et al. Risk factors for infection and treatment outcome of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in patients with hematologic malignancy. *Ann Hematol* 2012;91:115–21.
39. Wu YH, Chen PL, Hung YP, et al. Risk factors and clinical impact of levofloxacin or cefazolin nonsusceptibility or ESBL production among uropathogens in adults with community-onset urinary tract infections. *J Microbiol Immunol Infect* 2014;47:197–203.
40. Rodriguez-Bano J, Picon E, Gijon P, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli: risk factors and prognosis. *Clin Infect Dis* 2010;50:40–8.
41. Gurntke S, Kohler C, Steinmetz I, et al. Molecular epidemiology of extended-spectrum beta-lactamase (ESBL)-positive Klebsiella pneumoniae from bloodstream infections and risk factors for mortality. *J Infect Chemother* 2014;20:817–9.
42. Oh MM, Chae JY, Kim JW, et al. Positive culture for extended-spectrum beta-lactamase during acute prostatitis after prostate biopsy is a risk factor for progression to chronic prostatitis. *Urology* 2013;81:1209–12.
43. Leistner R, Gurntke S, Sakellariou C, et al. Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive K. pneumoniae and E. coli: an analysis of the disease burden in a large cohort. *Infection* 2014;42:991–7.

44. Ku NS, Chung HS, Choi JY, et al. Clinical usefulness of the 2010 clinical and laboratory standards institute revised breakpoints for cephalosporin use in the treatment of bacteremia caused by Escherichia coli or Klebsiella spp. *Biomed Res Int* 2015;2015:831074.
45. Anunnatsiri S, Towiwat P, Chaimanee P. Risk factors and clinical outcomes of extended spectrum beta-lactamase (ESBL)-producing Escherichia coli septicemia at Srinagarind University Hospital, Thailand. *Southeast Asian J Trop Med Public Health* 2012;43:1169–77.
46. Kang CI, Kim SH, Kim DM, et al. Risk factors for and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae. *Infect Control Hosp Epidemiol* 2004;25:860–7.
47. Raviv Y, Shitrit D, Amital A, et al. Multidrug-resistant Klebsiella pneumoniae acquisition in lung transplant recipients. *Clin Transplant* 2012;26:E388–94.
48. MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. *J Hosp Med* 2014;9:232–8.
49. Abhilash KP, Veeraraghavan B, Abraham OC. Epidemiology and outcome of bacteremia caused by extended spectrum beta-lactamase (ESBL)-producing Escherichia coli and Klebsiella spp. in a tertiary care teaching hospital in south India. *J Assoc Physicians India* 2010;58 Suppl:13-7.
50. Shanthi M, Sekar U. Extended spectrum beta lactamase producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *J Assoc Physicians India* 2010;58 Suppl:41–4.
51. Han SB, Jung SW, Bae EY, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in febrile neutropenic children. *Microb Drug Resist* 2015;21:244–51.
52. Lee S, Song DY, Cho SH, et al. Impact of extended-spectrum beta-lactamase on acute pyelonephritis treated with empirical ceftriaxone. *Microb Drug Resist* 2014;20:39–44.
53. Chayakulkeeree M, Junsriwong P, Keerasuntonpong A, et al. Epidemiology of extended-spectrum beta-lactamase producing gram-negative bacilli at Siriraj Hospital, Thailand, 2003. *Southeast Asian J Trop Med Public Health* 2005;36:1503–9.
54. Apisarnthanarak A, Kiratisin P, Mundy LM. Predictors of mortality from community-onset bloodstream infections due to extended-spectrum beta-lactamase-producing

Escherichia coli and Klebsiella pneumoniae. *Infect Control Hosp Epidemiol* 2008;29:671–4.

55. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Predictors of mortality among patients with community-onset infection due to extended-spectrum beta-lactamase-producing Escherichia coli in Thailand. *Infect Control Hosp Epidemiol* 2008;29:80–2.
56. Jean SS, Ko WC, Xie Y, et al. Clinical characteristics of patients with community-acquired complicated intra-abdominal infections: a prospective, multicentre, observational study. *Int J Antimicrob Agents* 2014;44:222–8.
57. Lee J, Pai H, Kim YK, et al. Control of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a children's hospital by changing antimicrobial agent usage policy. *J Antimicrob Chemother* 2007;60:629–37.
58. Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, et al. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. *Int J Clin Pract* 2012;66:891–6.
59. Ha YE, Kang CI, Cha MK, et al. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in patients with cancer. *Int J Antimicrob Agents* 2013;42:403–9.
60. Du B, Long Y, Liu H, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bloodstream infection: risk factors and clinical outcome. *Intensive Care Med* 2002;28:1718–23.
61. Stone PW, Gupta A, Loughrey M, et al. Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae outbreak in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2003;24:601–6.
62. Pena C, Pujol M, Ardanuy C, et al. An outbreak of hospital-acquired Klebsiella pneumoniae bacteraemia, including strains producing extended-spectrum beta-lactamase. *J Hosp Infect* 2001;47:53–9.
63. Kola A, Maciejewski O, Sohr D, et al. Clinical impact of infections caused by ESBL-producing E. coli and K. pneumoniae. *Scand J Infect Dis* 2007;39:975–82.
64. Tsai MH, Lee IT, Chu SM, et al. Clinical and Molecular Characteristics of Neonatal Extended-Spectrum beta-Lactamase-Producing Gram-Negative Bacteremia: A 12-Year Case-Control-Control Study of a Referral Center in Taiwan. *PLoS One* 2016;11(8):e0159744.

65. Maslikowska JA, Walker SA, Elligsen M, et al. Impact of infection with extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella species on outcome and hospitalization costs. *J Hosp Infect* 2016;92:33–41.
66. Onken A, Said AK, Jorstad M, et al. Prevalence and antimicrobial resistance of microbes causing bloodstream infections in Unguja, Zanzibar. *PLoS One* 2015;10:e0145632.
67. Nguyen ML, Toye B, Kanji S, et al. Risk factors for and outcomes of bacteremia caused by extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella species at a Canadian tertiary care hospital. *Can J Hosp Pharm* 2015;68(2):136–43. [published Online First: 2015/05/13]
68. Denis B, Lafaurie M, Donay JL, et al. Prevalence, risk factors, and impact on clinical outcome of extended-spectrum beta-lactamase-producing Escherichia coli bacteraemia: a five-year study. Int *J Infect Dis* 2015;39:1–6.
69. Chopra T, Marchaim D, Johnson PC, et al. Risk factors for bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: A focus on antimicrobials including cefepime. *Am J Infect Control* 2015;43:719–23.
70. Artero A, Esparcia A, Alberola J, et al. Prospective cohort study of risk factors for extended-spectrum ss-lactamase-producing Escherichia coli urinary tract infections in elderly patients admitted to hospital. *Int J Clin Pract* 2017;71:doi:10.1111/ijcp.13001
71. Chen IL, Huang HC, Wu CT, et al. Analysis of early-onset bloodstream infection due to Escherichia coli infection in premature babies. *Medicine* 2017;96:e7748.
72. Islas-Munoz B, Volkow-Fernandez P, Ibanes-Gutierrez C, et al. Bloodstream infections in cancer patients. Risk factors associated with mortality. *Int J Infect Dis* 2018;71:59–64.
73. Ma J, Li N, Liu Y, et al. Antimicrobial resistance patterns, clinical features, and risk factors for septic shock and death of nosocomial E coli bacteremia in adult patients with hematological disease: A monocenter retrospective study in China. *Medicine* 2017;96:e6959.
74. Man MY, Shum HP, Chan YH, et al. Clinical predictors and outcomes of Klebsiella pneumoniae bacteraemia in a regional hospital in Hong Kong. *J Hosp Infect* 2017;97:35–41.
75. Marando R, Seni J, Mirambo MM, et al. Predictors of the extended-spectrum-beta lactamases producing Enterobacteriaceae neonatal sepsis at a tertiary hospital, Tanzania. *Int J Med Microbiol* 2018;308:803–11.

76. Namikawa H, Yamada K, Fujimoto H, et al. Clinical characteristics of bacteremia caused by extended-spectrum beta-lactamase-producing Escherichia coli at a tertiary hospital. *Intern Med* 2017;56:1807–15.
77. Shi SH, Feng XN, Lai MC, et al. Biliary diseases as main causes of pyogenic liver abscess caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Liver Int* 2017;37:727–34.
78. Tanir Basaranoglu S, Ozsurekci Y, Aykac K, et al. A comparison of blood stream infections with extended spectrum beta-lactamase-producing and non-producing Klebsiella pneumoniae in pediatric patients. *Ital J Pediat* 2 017;43:79.
79. Razazi K, Mekontso Dessap A, Carteaux G, et al. Frequency, associated factors and outcome of multi-drug-resistant intensive care unit-acquired pneumonia among patients colonized with extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Ann Intensive Care* 2017;7:61.
80. Ray S, Anand D, Purwar S, et al. Association of high mortality with extended-spectrum beta-lactamase (ESBL) positive cultures in community acquired infections. *J Crit Care* 2018;44:255–60.
81. Haruki Y, Hagiya H, Haruki M, et al. Clinical characteristics and outcome of critically ill patients with bacteremia caused by extended-spectrum beta-lactamase-producing and non-producing Escherichia coli. *J Infect Chemother* 2018;24:944–7.
82. Lin WT, Tang HJ, Lai CC, et al. Clinical manifestations and bacteriological features of culture-proven Gram-negative bacterial arthritis. *J Microbiol Immunol Infect* 2017;50:527–31.
83. Buys H, Muloiwa R, Bamford C, et al. Klebsiella pneumoniae bloodstream infections at a South African children's hospital 2006-2011, a cross-sectional study. BMC Infect Dis 2016;16:570.
84. Lee CC, Lee CH, Hong MY, et al. Propensity-matched analysis of the impact of extended-spectrum beta-lactamase production on adults with community-onset Escherichia coli, Klebsiella species, and Proteus mirabilis bacteremia. *J Microbiol Immunol Infect* 2018;51:519–26.
85. Huang YY, Alleyne A, Leung V, et al. Urosepsis due to extended-ppectrum beta-lactamase-producing Escherichia coli: a retrospective, single-centre review of risk Factors and clinical outcomes. *Can J Hosp Pharm* 2018;71:119-27.

86. Komatsu Y, Kasahara K, Inoue T, et al. Molecular epidemiology and clinical features of extended-spectrum beta-lactamase- or carbapenemase-producing Escherichia coli bacteremia in Japan. *PLoS One* 2018;13:e0202276.
87. Liu M, Li M, Wu L, et al. Extended-spectrum beta-lactamase-producing E. coli septicemia among rectal carriers in the ICU. *Medicine* 2018;97:e12445.
88. Nivesvivat T, Piyaraj P, Thunyaharn S, et al. Clinical epidemiology, risk factors and treatment outcomes of extended-spectrum beta-lactamase producing Enterobacteriaceae bacteremia among children in a tertiary care hospital, Bangkok, Thailand. *BMC Res Notes* 2018;11:624.
89. Cordery RJ, Roberts CH, Cooper SJ, et al. Evaluation of risk factors for the acquisition of bloodstream infections with extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in the intensive care unit; antibiotic management and clinical outcome. *J Hosp Infect* 2008;68:108–15.
90. Daikos GL, Kosmidis C, Tassios PT, et al. Enterobacteriaceae bloodstream infections: presence of integrons, risk factors, and outcome. *Antimicrob Agents Chemother* 2007;51:2366–72. doi: 10.1128/AAC.00044-07 [published Online First: 2007/04/25]
91. Gudiol C, Calatayud L, Garcia-Vidal C, et al. Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. *J Antimicrob Chemother* 2010;65(2):333–41.
92. Marchaim D, Gottesman T, Schwartz O, et al. National multicenter study of predictors and outcomes of bacteremia upon hospital admission caused by Enterobacteriaceae producing extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2010;54:5099–104.
93. Menashe G, Borer A, Yagupsky P, et al. Clinical significance and impact on mortality of extended-spectrum beta lactamase-producing Enterobacteriaceae isolates in nosocomial bacteremia. *Scand J Infect Dis* 2001;33:188–93.
94. Ortega M, Marco F, Soriano A, et al. Analysis of 4758 Escherichia coli bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. *J Antimicrob Chemother* 2009;63:568–74.
95. Szilagyi E, Fuzi M, Borocz K, et al. Risk factors and outcomes for bloodstream infections with extended-spectrum beta-lactamase-producing Klebsiella pneumoniae ; Findings of the nosocomial surveillance system in Hungary. *Acta Microbiol Immunol Hung* 2009;56:251–62. doi:

96. Tsai SS, Huang JC, Chen ST, et al. Characteristics of Klebsiella pneumoniae bacteremia in community-acquired and nosocomial infections in diabetic patients. *Chang Gung Med J* 2010;33:532–9.

97. Carrara E, Pfeffer I, Zusman O, et al. Determinants of inappropriate empirical antibiotic treatment: systematic review and meta-analysis. *Int J Antimicrob Agents* 2018;51:548–53,

98. Horcajada JP, Shaw E, Padilla B, et al. Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective multicentre cohort study in the era of antimicrobial resistance. *Clin Microbiol Infect*. 2013 Oct;19(10):96

99. Pitout JD, Nordmann P, Laupland KB et al. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. J Antimicrob Chemother 2005; 56: 52-59. doi:10.1093/jac/dki166

100. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 2008; 8: 159-166. doi:10.1016/S1473-3099(08)70041-0

101. Palacios-Baena ZR, Gutierrez-Gutierrez B, De Cueto M et al. Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-beta-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2017; 72: 906-913. doi:10.1093/jac/dkw513

102. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clin Microbiol Infect* 2014;20:973–80.

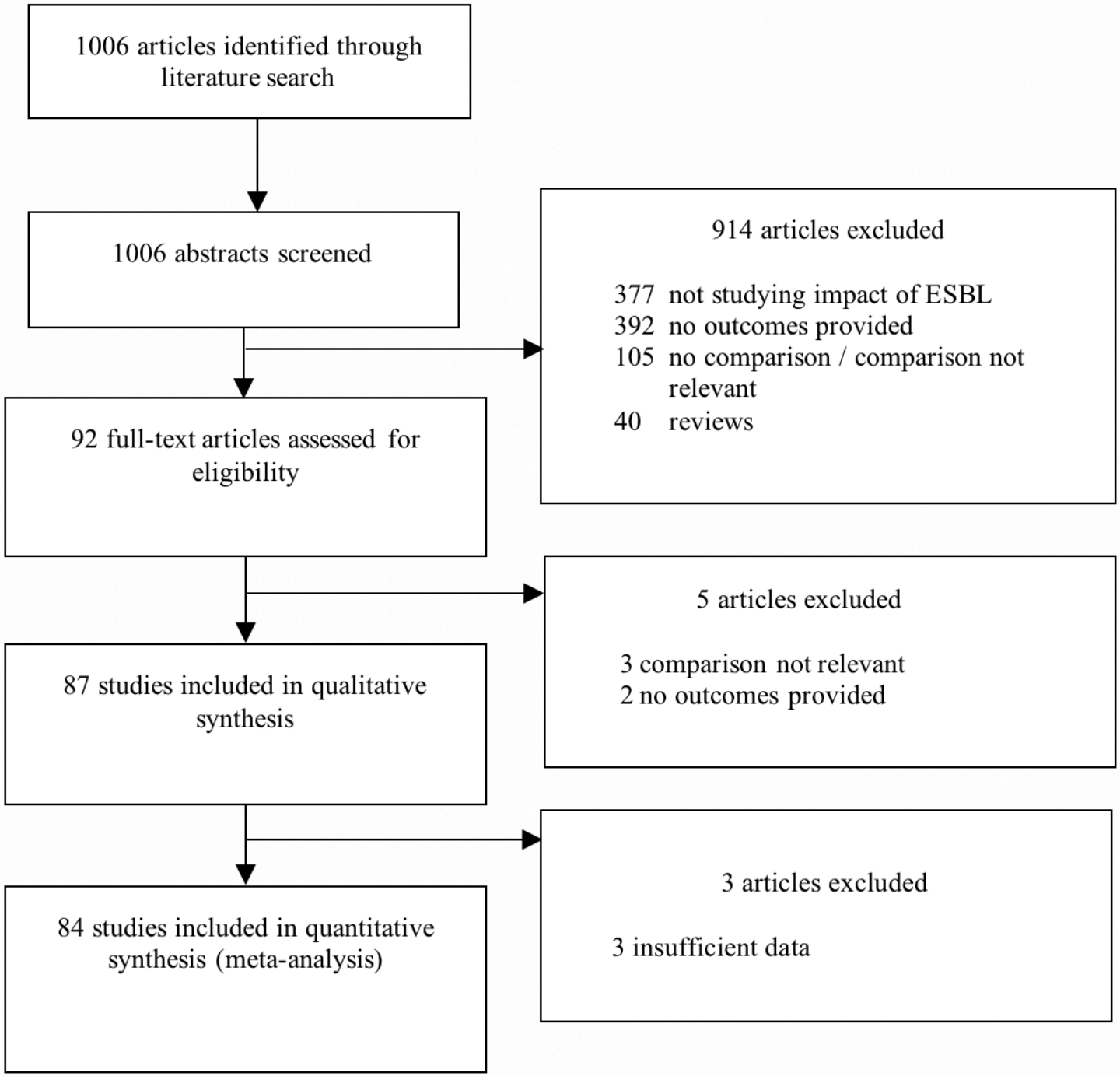
FIGURE LEGENDS

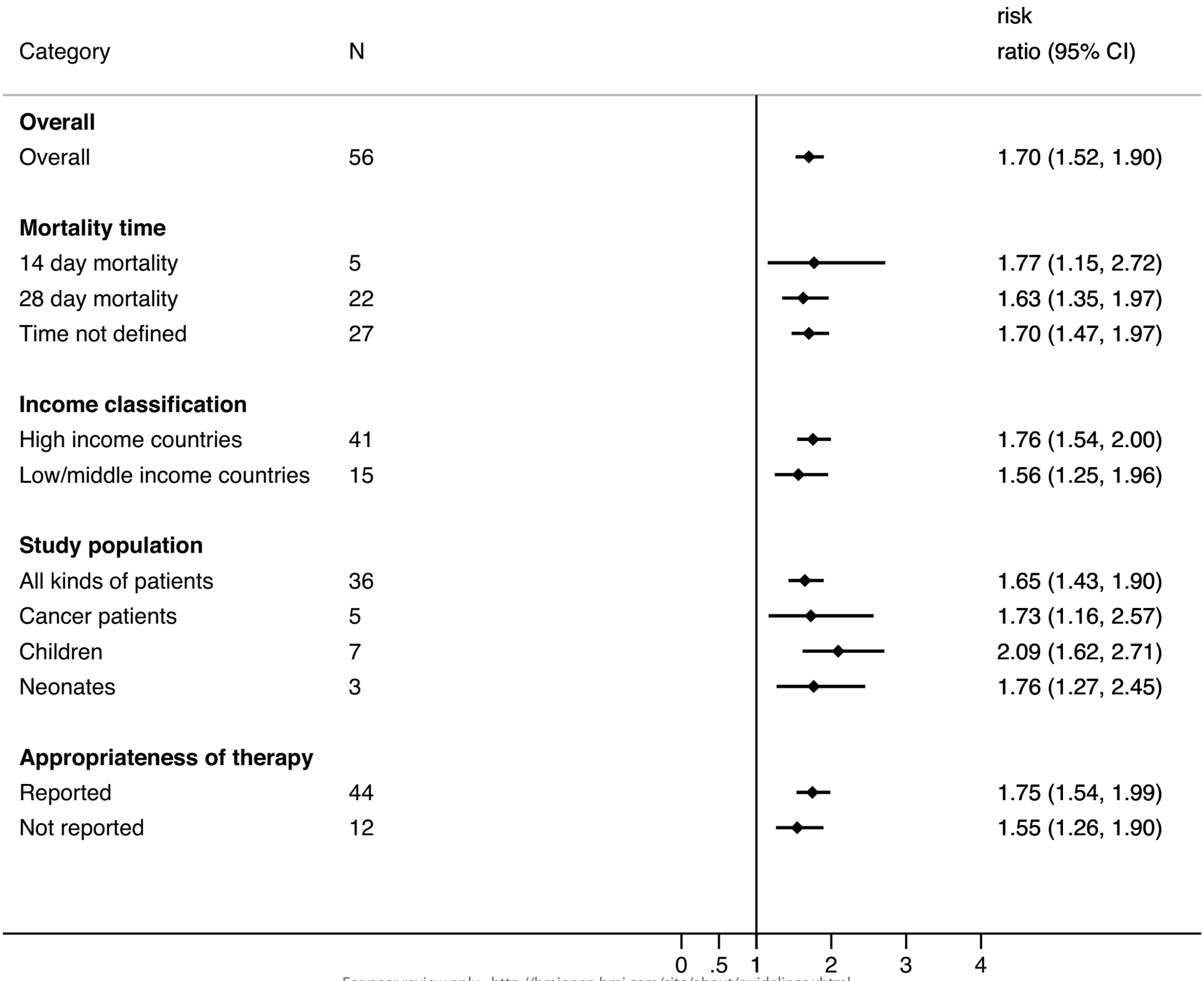
Figure 1: Literature search and study inclusion and exclusion

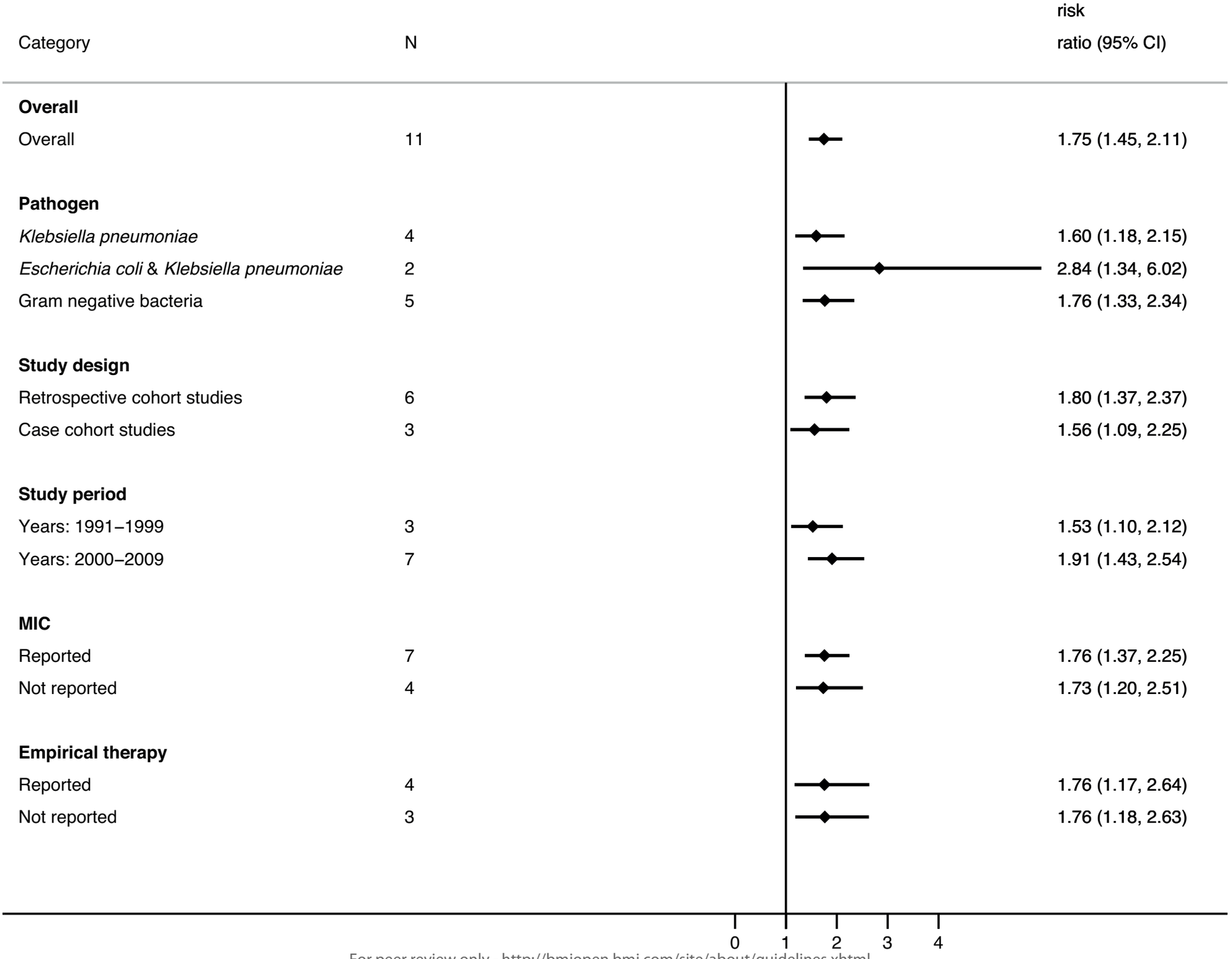
Figure 2: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections— subgroups not included in attributable mortality

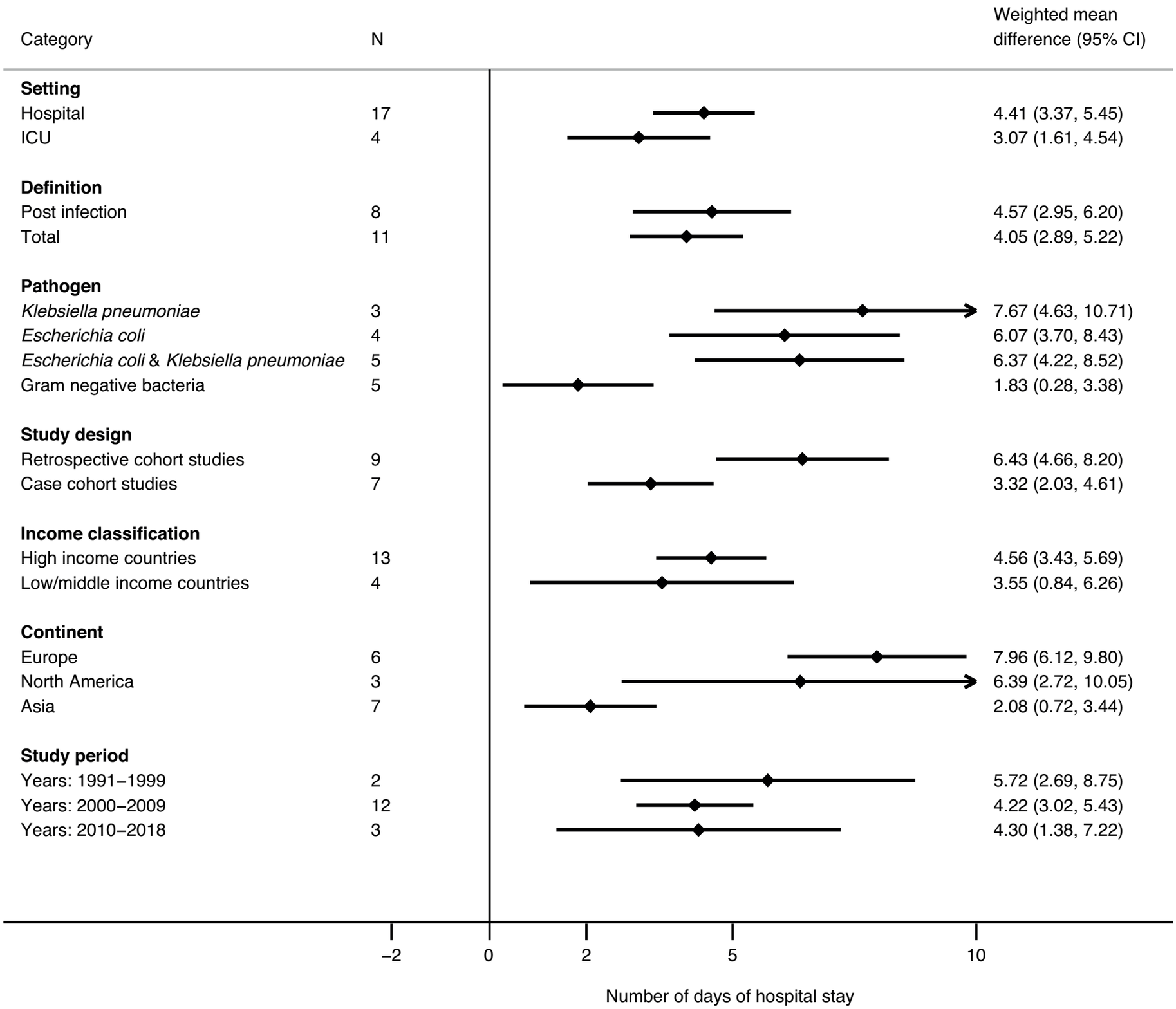
Figure 3: Pooled risk ratios for attributable mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

Figure 4: Weighted mean difference in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

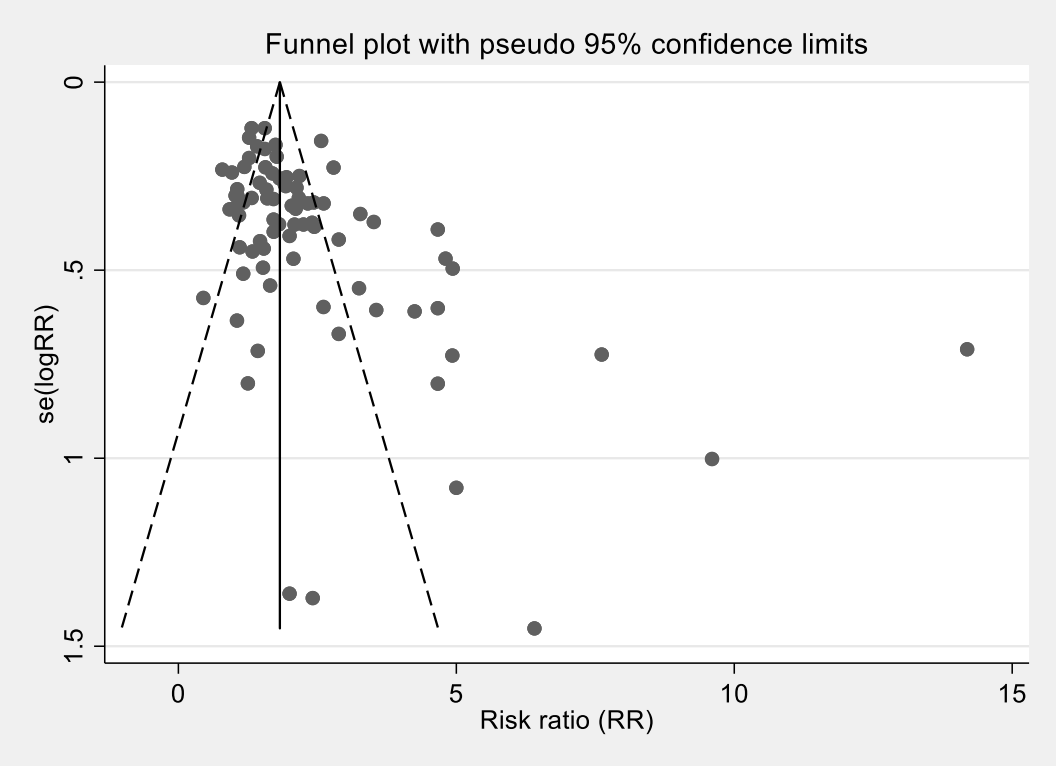

1006 articles identified through literature search
1006 abstracts screened
914 articles excluded
377 not studying impact of ESBL
392 no outcomes provided
105 no comparison / comparison not relevant
40 reviews
92 full-text articles assessed for eligibility
5 articles excluded
3 comparison not relevant
2 no outcomes provided
87 studies included in qualitative synthesis
3 articles excluded
3 insufficient data
84 studies included in quantitative synthesis (meta-analysis)




Category
N
risk ratio (95% CI)
Overall
Overall 11 1.75 (1.45, 2.11)
Pathogen
Klebsiella pneumoniae 4 1.60 (1.18, 2.15)
Escherichia coli & Klebsiella pneumoniae 2 2.84 (1.34, 6.02)
Gram negative bacteria 5 1.76 (1.33, 2.34)
Study design
Retrospective cohort studies 6 1.80 (1.37, 2.37)
Case cohort studies 3 1.56 (1.09, 2.25)
Study period
Years: 1991–1999 3 1.53 (1.10, 2.12)
Years: 2000–2009 7 1.91 (1.43, 2.54)
MIC
Reported 7 1.76 (1.37, 2.25)
Not reported 4 1.73 (1.20, 2.51)
Empirical therapy
Reported 4 1.76 (1.17, 2.64)
Not reported 3 1.76 (1.18, 2.63)
0
1
2
3
4

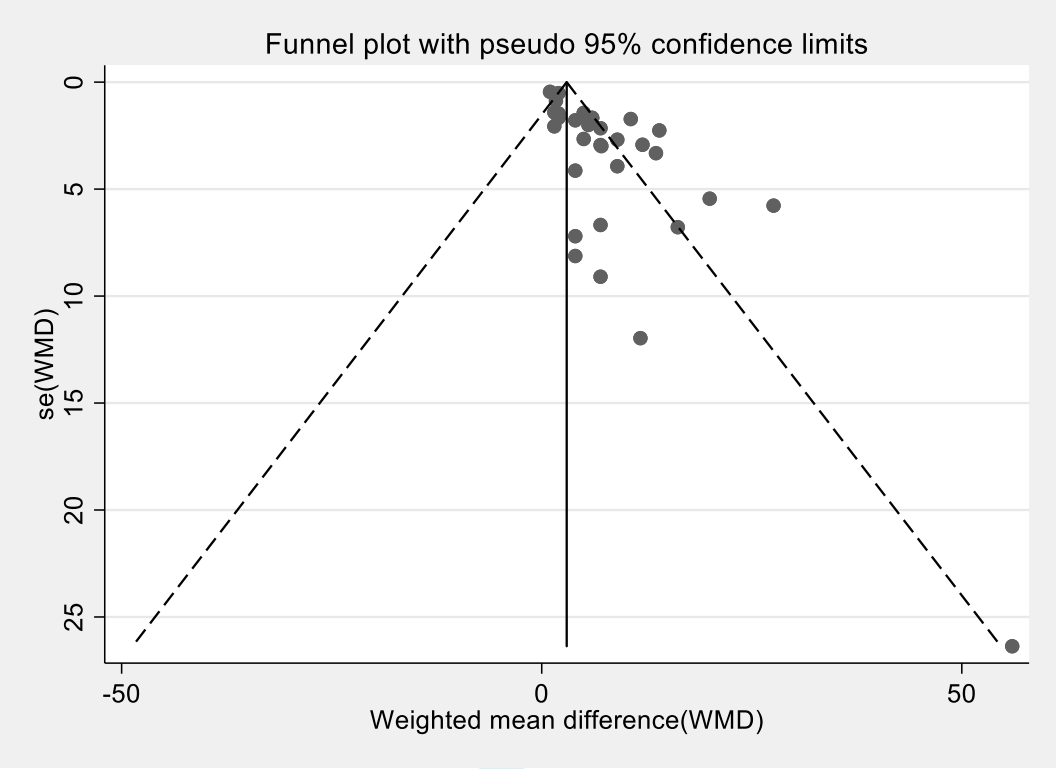

Category
N
Weighted mean difference (95% CI)
Setting
Hospital 17 4.41 (3.37, 5.45)
ICU 4 3.07 (1.61, 4.54)
Definition
Post infection 8 4.57 (2.95, 6.20)
Total 11 4.05 (2.89, 5.22)
Pathogen
Klebsiella pneumoniae 3 7.67 (4.63, 10.71)
Escherichia coli 4 6.07 (3.70, 8.43)
Escherichia coli & Klebsiella pneumoniae 5 6.37 (4.22, 8.52)
Gram negative bacteria 5 1.83 (0.28, 3.38)
Study design
Retrospective cohort studies 9 6.43 (4.66, 8.20)
Case cohort studies 7 3.32 (2.03, 4.61)
Income classification
High income countries 13 4.56 (3.43, 5.69)
Low/middle income countries 4 3.55 (0.84, 6.26)
Continent
Europe 6 7.96 (6.12, 9.80)
North America 3 6.39 (2.72, 10.05)
Asia 7 2.08 (0.72, 3.44)
Study period
Years: 1991–1999 2 5.72 (2.69, 8.75)
Years: 2000–2009 12 4.22 (3.02, 5.43)
Years: 2010–2018 3 4.30 (1.38, 7.22)
−2
0
2
5
10
Number of days of hospital stay

Supplementary figure 1: Funnel plot of risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



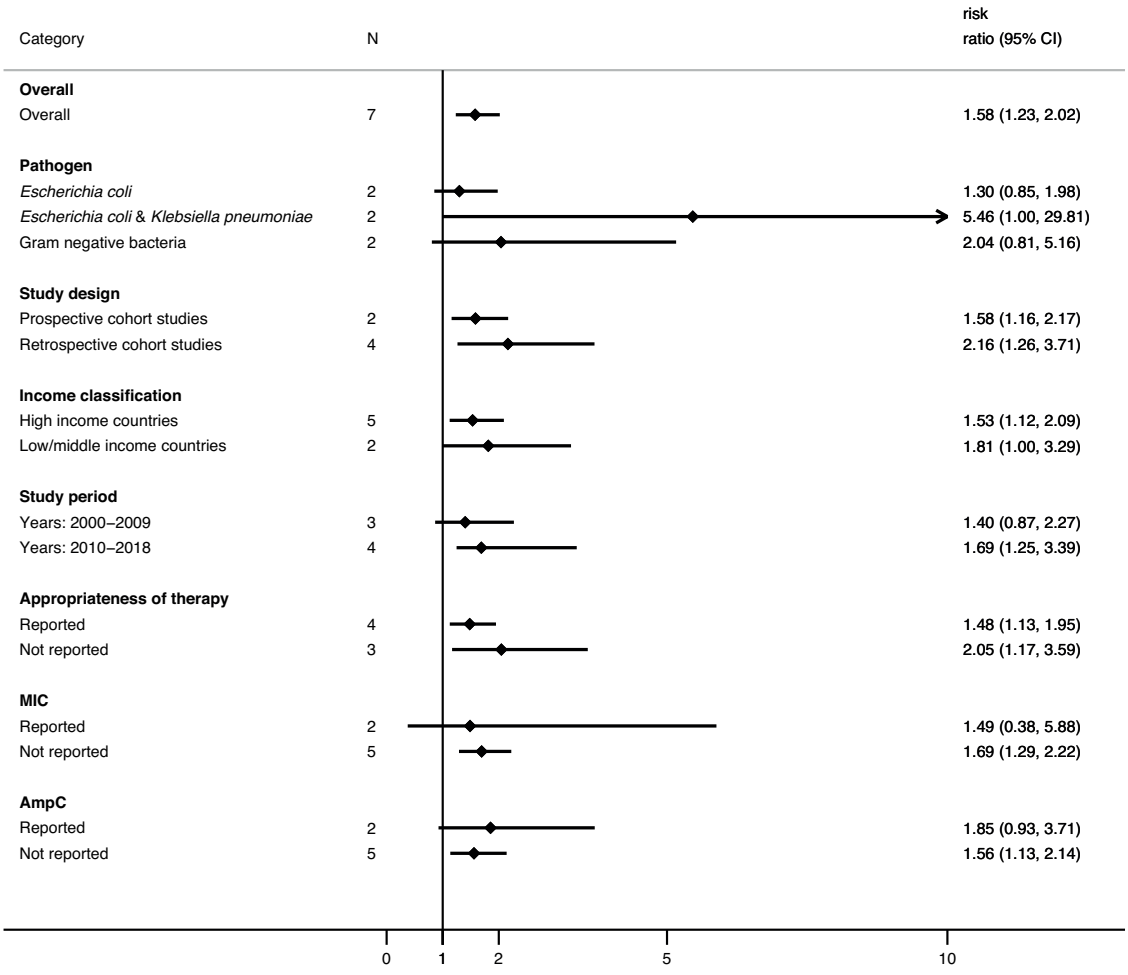
The y axis se(logRR) is the standard error of the log risk ratio Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 2: Funnel plot of weighted mean differences in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

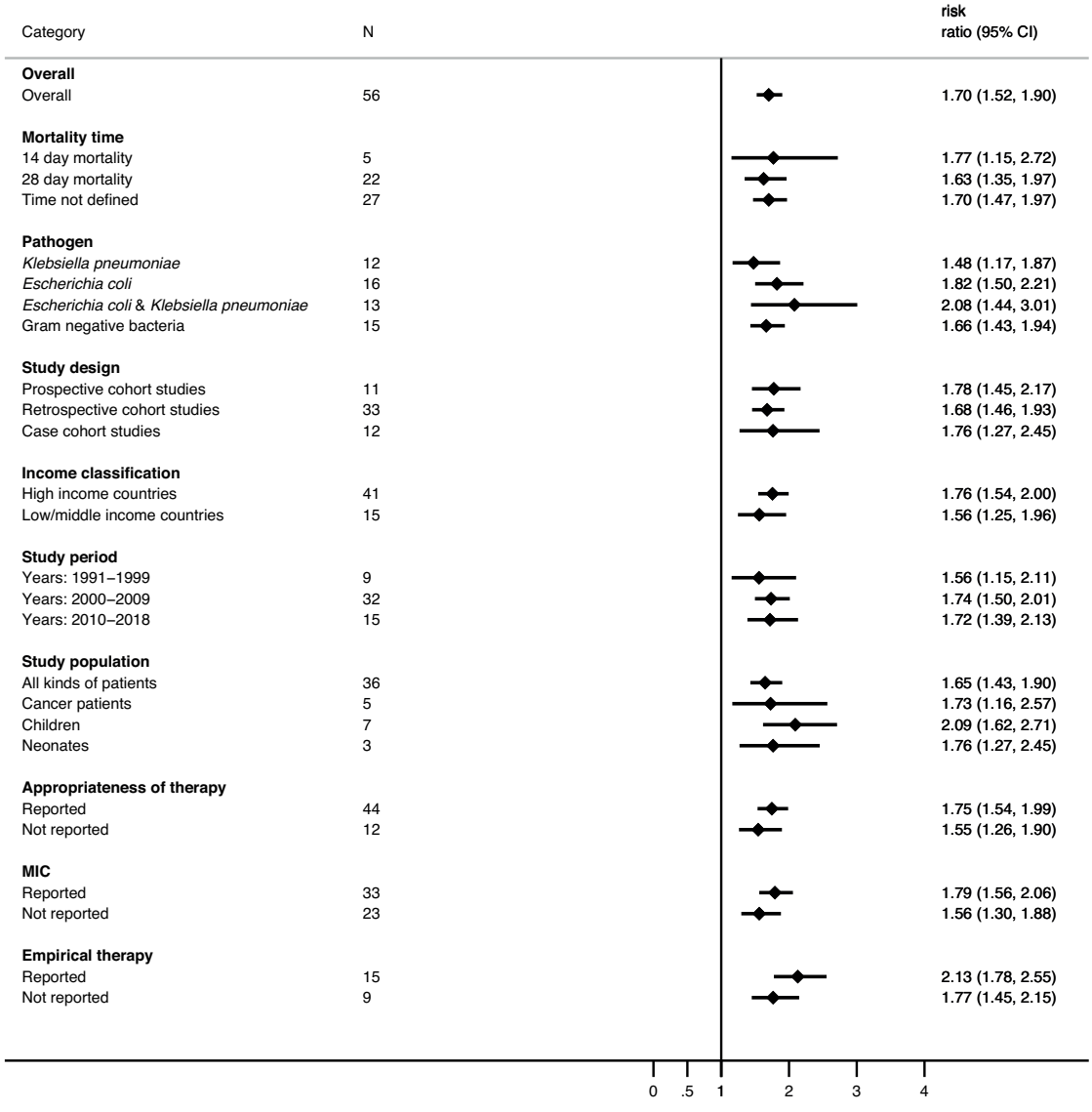


The y axis se(WMD) is the standard error of the weighted mean difference. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

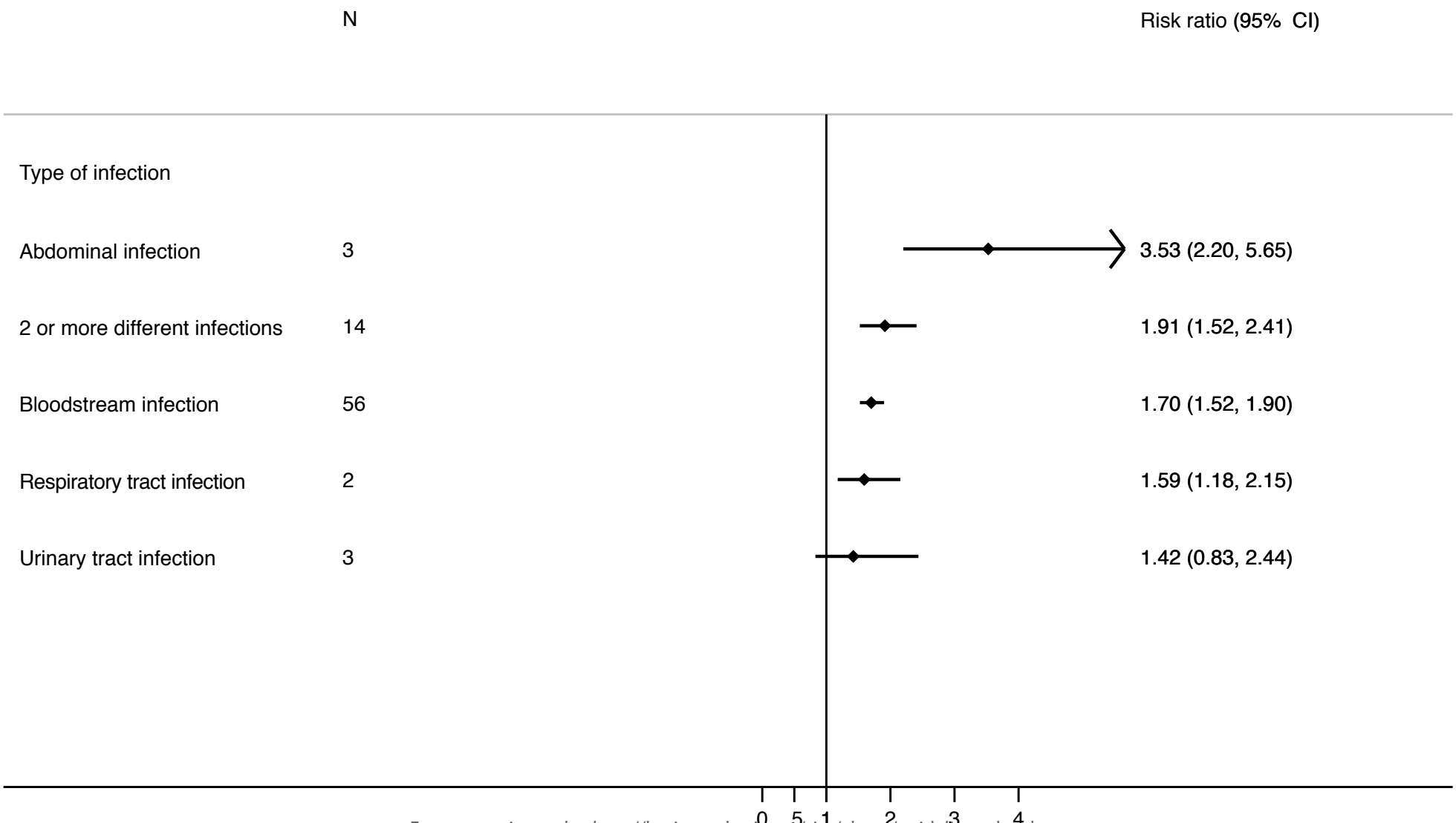
Supplementary figure 3: Pooled risk ratios for all-cause mortality in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



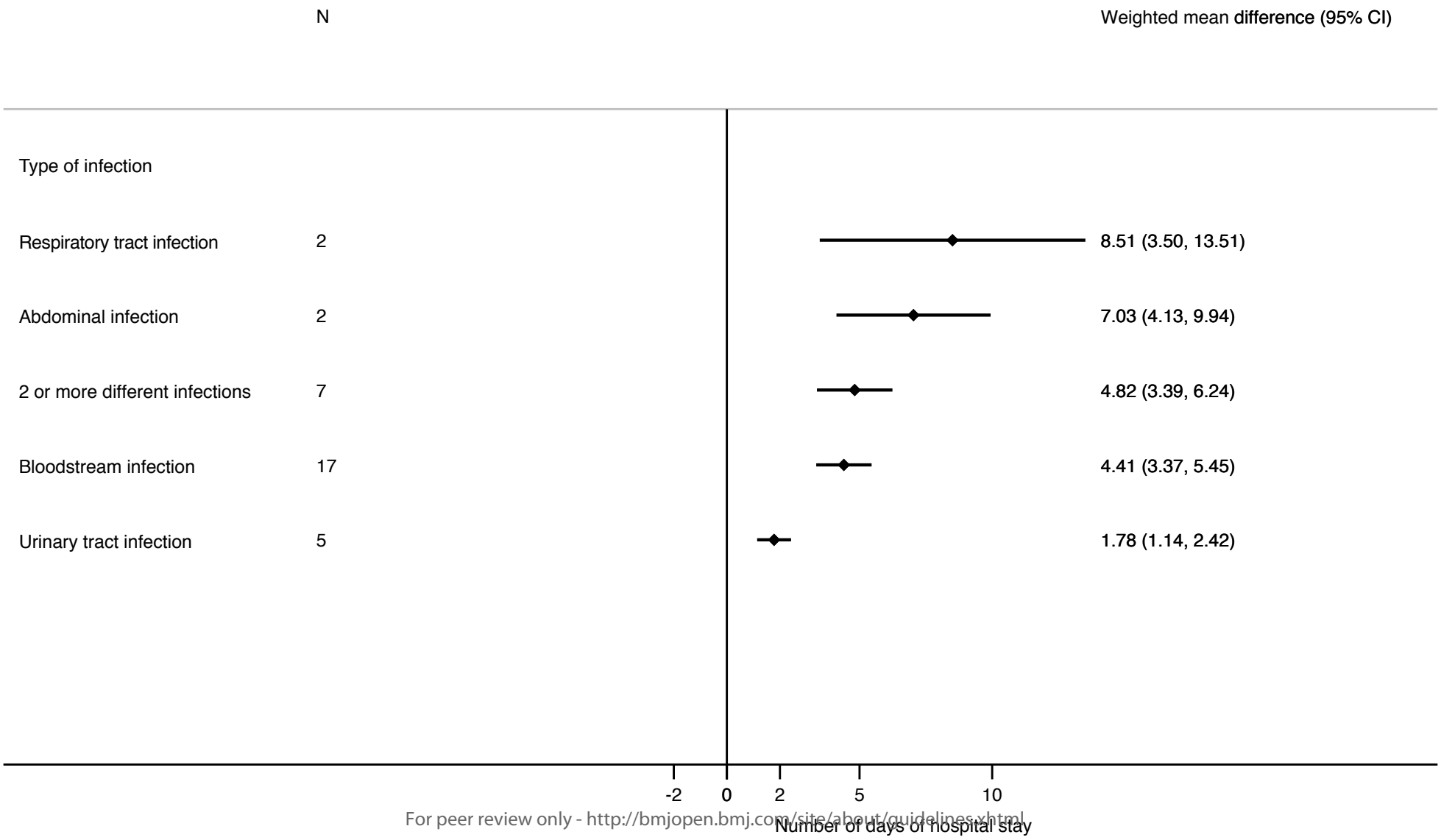
Supplementary figure 4: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections—all subgroups



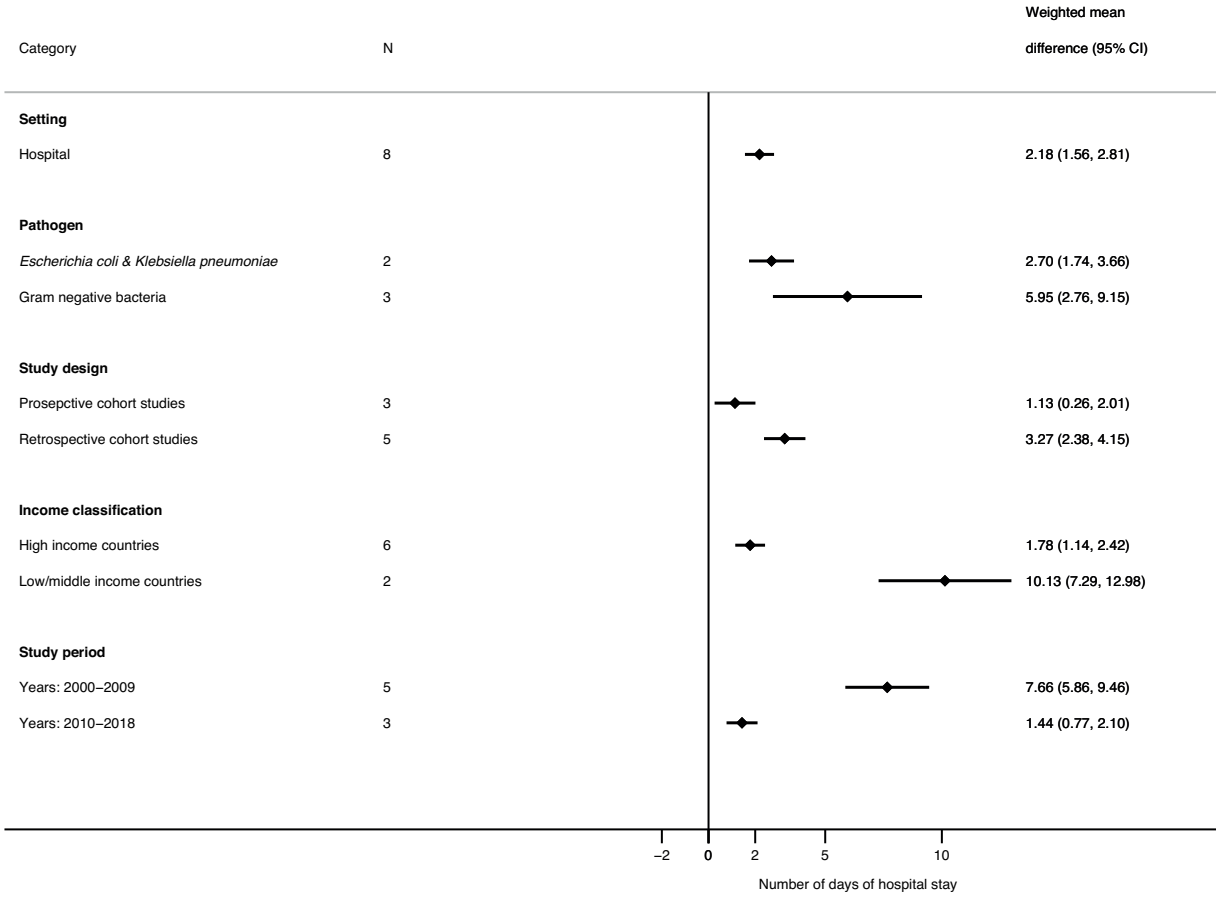
Supplementary figure 5: Pooled risk ratios for all-cause mortality stratified by type of infection



Supplementary figure 6: Weighted mean differences in length of hospital stay stratified by type of infection



Supplementary figure 7: Weighted mean differences in length of hospital stay in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary table S1: Search terms used in PubMed :

((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh])

AND

(Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])) OR (Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])

Coupled with

(length of stay[mesh] OR (hospitalisation[tw] AND length[tw]) OR length of hospitalisation[tw] OR length of hospitalization[tw] OR duration of hospitalization[tw] duration of hospitalisation[tw] OR LOS[tw] OR ((period[tw] OR length[tw]) AND (hospital stay[tw] OR hospitalisation[tw] OR hospitalization[tw]) OR

(mortality[mesh] OR mortality[tw] OR death rate[tw] OR fatality[tw] OR survival rate[tw] OR death[tw] OR died[tw] OR dead[tw])))) OR

(cost[Title/Abstract] OR"costs and cost analysis"[MeSH:noexp])*

Coupled with

("0001/01/01"[PDat] : "2018/10/01"[PDat]))

Supplementary table S2: Modified Newcastle Ottawa quality assessment scale for case-control studies and cohort studies.

	For case cohort studies, the quality criteria assessed are		
1	**Is the case definition adequate?**	a*	yes, with independent validation
		b	yes, eg. record linkage or based on self-report
		c	no description
2	**Representativeness of the cases**	a*	consecutive or obviously representative series of cases
		b	potential for selection biases or not stated
3	**Selection of Controls**	a*	community controls
		b	hospital controls
		c	no description
4	**Definition of Controls**	a*	no history of disease (endpoint)
		b	no description of source
5	**Comparability of cases and controls on the basis of the design or analysis**	a*	study controls for at least one variable (including age, sex and comorbidities)
		b**	study controls for more than one variable (including age, sex and comorbidities)
6	**Ascertainment of exposure**	a*	secure record (eg surgical records)
		b	structured interview blind to case/control status
		c	interview not blinded to case/control status
		d	written self-report or medical record only
		e	no description
7	**Same method of ascertainment for cases and controls**	a*	yes
		b	no
		c	unclear
8	**Non-Response rate**	a	same rate for both groups
		b	non respondents described
		c	rate different and no designation
	For cohort studies, the quality criteria assessed are		
1	**Representativeness of the exposed cohort**	a*	truly representative
		b*	somewhat representative
		c	selected group of users
		d	no description
2	**Selection of the non-exposed cohort**	a*	drawn from the same community as the exposed cohort
		b	drawn from a different source
		c	no description of the derivation of the non-exposed cohort
3	**Ascertainment of exposure**	a*	secure record (eg surgical records)
		a*	structured interview
		c	written self-report
		d	no description
4	**Demonstration that outcome of interest was not present at start of study**	a*	yes
		b	no
		c	unclear
5	**Comparability of cohorts on the basis of the design or analysis**	a*	study controls for age or comorbidities
		b**	study controls for age and comorbidities
6	**Assessment of outcome:**	a*	independent blind assessment
		b*	record linkage
		c	self-report
		d	no description

7	**Follow-up long enough for outcomes to occur**	a*	yes
		b	no
		c	unclear
8	**Adequacy of follow up of cohorts**	a*	complete follow up – all that matters subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number
		b*	inadequate numbers but description provided of those lost
		c	inadequate follow up rate and no description of those lost
		d	no statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Supplementary table S3: Study characteristics overview

Subgroup	All Studies	Bloodstream infections	Noninvasive infections
	87	**57**	**10**
Country			
South Korea [13,14,16,17,31,35,38,42,44,46,51,52,57,59]	14	9	2
Thailand[24,26,45,53-55,88]	7	3	
USA[10,18,28,32,48,61,69]	7	2	1
Spain [36,40,58,62,70,91,93]	7	4	2
Taiwan [12,39,64,71,82,84,96]	7	5	2
China [60,73,74,76,86]	5	4	
Israel [23,47,92,93]	4	3	
Germany [10,40,43,63]	4	3	
Italy [25,33,37]	3	3	
Japan [76,81,86]	3	3	
Tanzania [19,66,75]	3	3	
India [49,50,80]	3	1	1
Canada [65,67,85]	3	2	
UK [22,30,89]	3	3	
France [68,79]	2	1	1
South Africa [13,81]	2	1	
Brazil [21,34]	2	2	
Greece [90]	1	1	
Hungary [95]	1	1	
Lebanon [27]	1	-	
Malaysia [29]	1	-	1
Mexico [72]	1	1	
Saudi Arabia [20]	1	1	
Turkey [78]	1	1	
Continent			
Asia [12-14,16,17,20,23,24,25,27,29,31,35,38,39,42,44-47,49, 55,57,59,60,64,71,73,74,76,80-82 ,84,86-88,92,93,96]	46	29	6
Europe [11,22,25,30,33,35,37,40,41,43,58,62,63,68,70,78,79,89-91,94,95]	22	17	3
North America [10,18,28,32,48,61,65,67,69,85]	10	4	1
Africa [15,19,66,75,83]	5	4	-
South America [21,34,72]	3	3	-
More than 1 continent [56]	1	-	-

Income group			
High-income countries [10-14,16-18,20,22,23,25,28,30-33,35-44,46-48,51,52,57-59,61-65,67-71,76,79,81,82,84-86,89-96,]	60	41	8
Low- and middle-income countries [15,19,21,23,25,27,29,34,45,50,53-55,60,66,72-75,77,78,80,83,87,88]	26	16	2
High-income countries AND Low- and middle-income countries [56]	1	-	-
Study design			
Case cohort study [10,12,24-28,31,40,44,46,55,58,61,63-65,67-69,85-87]	24	14	
Retrospective cohort study [11,13-17,20,21,23,29,33-38,41-43,45,47,48,50-54,59,60,71,73,74,76-78,81-84,88,89,93,95,96]	44	32	
Prospective cohort study [18,19,30,32,39,49,56,62,66,70,72,75,79,80,90-92,94]	18	11	
Year group			
1991-1999[10,60,15,16,17,62,21,25,28,36,46,93,94]	13	10	-
2000-2009 [11-14,18-20,22-24,26,27,29-35,37-45,47,49-52,54,55,57,58,61,63,64,67-69,89-92,95,96]	49	31	6
2010-2018 [48,53,54,59,65,66,70-88]	25	16	4
Pathogen			
Escherichia coli [11,24,30,33,35-37,40,43,45,52,55,58,59,68,70,71,73,76,86,87,91,94]	23	16	3
Klebsiella pneumoniae [15,16,20,21,25,29,32,34,41,43,47,61,62,74,78,83,95,96]	17	11	1
E. coli and *K. pneumoniae* [10,13,14,17,26,28,38,43,44,46,48,50,51,54,57,60,63,69,85,88,89]	20	13	2
Gram-negative bacteria [12,18,19,22,23,27,31,39,42,49,53,56,64-67,72,75,77,79-82,84,90,92,93]	27	17	4
Study setting			
Entire hospital[1011,16,18,20-27,29,30,33-38,40-46,48-50,52-55,58-60,62,65-69,73,74,76,82,85,86,90-96]	57	40	7
Intensive care unit [32,61,64,75,79-81,88,89]	9	5	1
Pediatric ward [17,19,28,51,57,78,83,88]	8	7	-
Neonatal ward [15,61,64,71,75]	5	3	-
Neonatal intensive care unit [61,64,75]	3	2	-
Medical ward [13,39,70]	3	-	2
Not provided [31,47]	2	-	-
Emergency Department [12,84]	2	2	-
Surgical ward [32,56]	2	-	-
Burn unit [32]	1	-	-
Oncology [72]	1	1	-
Referral centre for hepatopacreaticobiliary diseases [77]	1	-	-
Hematological [14]	1	1	-

Study population			
All kinds of patients[10-13,14,18,20-27,29,30,34,35,39-41,43-46,48-50,52-56,58,60,62,63,65-69,76,82,84-86,90,92-95]	55	36	7
Intensive care unit patients [32,79-81,87,89]	6	3	1
Children [17,19,28,51,57,78,83,88]	8	7	-
Neonates [15,61,64,71,75]	5	3	-
Cancer patients [33,51,59,72,91]	5	5	-
Immunocompromised patients [51]	1	1	-
Diabetic patients [96]	1	1	-
Elderly patients [70]	1	-	1
Patients with chemotherapy/stem cell transplantation [14,91]	2	2	-
Patients after prostatitis biopsy [42]	1	-	1
Lungs transplantation patients [47]	1	-	-
Hematological patients [73]	1	1	-
All except cardiothoracic therapy, transplant surgery, burns [74]	1	1	
Patients with pyogenic liver abscess [77]	1	-	-
Data reported			
Treatment information [10,12-13,23-25,30-38,40,44-49,51,52,54-65,67,68,70-96]	74	50	6
Appropriateness of treatment[10,12-14,16,17,19-21,23-26,30-38,40,44-46,48,49,51,52,54-56,58-60,62-65,67,68,70,72-74,76,77,79,81,83-86,89-96]	62	45	5
Empirical therapy [14,16,17,24,25,33,35-38,40,44,51,52,56,58,59,63,76,81,83,94]	22	16	2
Treatment outcome [10,12-21,25,26,30-38,40,44-49,51,52,54-57,59-65,67,68,72-74,76,78-81,83-86,88-92,94-96]	64	45	3
Minimum inhibitory concentration results [10,11,13,14,16-19,22-25,27,28,32,33,35-41,43,44,47,50-52,54-59,62,63,66,68,69,76-78,80,81,83,85-87,89,94,95]	52	34	4
AmpC genotyping [10,11,17,32,41,46,50,56,57,65,66,70,86]	13	6	2

Supplementary table S4: Characteristics for each study

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Lautenbach E[10]	1997-1998	USA	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality; LOS	Risk factors for infection with ESBL-producing pathogens, difference in clinical outcomes of infections: resistant vs. susceptible organisms	EC, KP
Kim SH[14]	2007-2008	South Korea	Cohort study, Retrospective	Non-ESBL-infection	Patients who received either chemotherapy or stem cell transplantation; neutropenic fever	Hematological ward, Others	All-cause mortality (28 day)	Risk factors for acquisition of ESBL, appropriateness of empirical antimicrobial therapy, clinical outcomes in relation to ESBL production	EC, KP
Chayakulkeere M[53]	2015-2015	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Prevalence & risk factors for infections with & antibiotic susceptibility patterns of & outcomes of patients infected with ESBL-producing-GNB	GNB
Apisarnthanarak A[54]	2003-2007	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Predictors for mortality associated with community-onset BSI with ESBL-producing pathogens, initial empirical antimicrobial regimens, associated hospital resource utilisation,costs accrued after diagnosis of BSI	EC, KP
Apisarnthanarak A[55]	2003-2004	Thailand	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Mortality associated with community-onset infection due to ESBL-producing pathogens, associated hospital resource use, post-infection hospital cost	EC
Jean SS[56]	2010-2011	Portugal, Columbia, the Philippines, Taiwan, Thailand	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Surgical ward	Attributable mortality, LOS	Clinical impact on hospitalised patients with community-acquired complicated intra-abdominal infection: ESBL-producing- vs. non-ESBL-producing pathogens	GNB
Lee J[57]	1999-2005	South Korea	interventional studies	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	impact of a change in antibiotic policy on ESBL-prevalence	EC, KP
Briongos-Figuero L.S[58]	2009-2010	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Characteristics &associated risk factors for EBSL-enterobacteria-UTIs	EC
Ha YE[59]	2010-2012	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with cancer	Entire hospital	All-cause mortality (28 day)	Clinical &molecular epidemiology of ESBL-EC bacteraemia, clinical impact of ESBLs on patient outcome	EC
Du B[60]	1997-1999	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for nosocomial ESBL-EC- and ESBL-KP- bacteraemia & influence on patient outcome.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Stone PW[61]	2001	USA	Case cohort study	Non-ESBL-infection	Neonates at NICU	NICU	LOS	costs of interventions aimed at controlling the outbreak, attributable length of stay associated with infection and colonisation with ESBL-KP	KP
Pillay T[15]	1995-1996	South Africa	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Use of piperacillin/tazobactam in treatment of KP- infection	KP
Kim BN[16]	1999-2000	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, LOS	Prevalence & clinical characteristics of ESBL-KP- bacteraemia, impact of ESBL- production on outcome of patients with KP-bacteraemia in endemic situation.	KP
Kim YK[17]	1993-1998	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Risk factors & clinical outcomes & clinical responses to treatment of ESBL-EC- and ESBL-KP-bacteraemia, prevalence and types of their ESBLs	EC, KP
Bhavnani SM[18]	2001-2002	USA	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Risk factors for occurrence of invasive ESBL-EC- and ESBL-KP-infections, factors associated with clinical outcome, drug regimens for treatment of infections associated ESBL/non-ESBL strains in real-life clinical practice, clinical response rates for patients treated with cephalosporins/other classes of antimicrobial agents, /carbapenems, clinical response for those patients with infection associated with ESBL and non–ESBL-producing strains with MIC values V8 Ag/mL treated with cephalosporins.	GNB
Blomberg B[19]	2001-2002	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates, children	Pediatric ward	All-cause mortality	Prevalence & clinical implications of ESBL production in EC-,KP-, Salmonellae- septicemia	GNB
Pena C[62]	1993-1995	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Clinical epidemiology& outcome of ESBL-KP- bacteraemia, relevance of ESBL strains in mortality of patients with hospital-acquired KP-BSI.	KP
Kola A[63]	2002-2004	Germany	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Outcomes of ESBL-EC- and ESBL-KP-infections	EC, KP
Tsai MH[64]	2001-2012	Taiwan	Case cohort study	Control group: non-ESBL-infection, second control group: all hospitalised patients	Neonates at NICU	NICU	Attributable mortality, all-cause mortality, LOS	Clinical features& risk factors& molecular epidemiology of ESBL-GNB	GNB
Maslikowska JA[65]	2010-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	Differences in clinical & microbiological outcome, mortality, and/or hospital resource use: ESBL-EC- and ESBL-Ks- vs non-ESBL-EC- and non-ESBL-Ks-infections	GNB

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Onken A[66]	2012-2013	Tanzania	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Most common bacterial pathogens causing BSI, antimicrobial susceptibility	GNB
Nguyen ML[67]	2005-2010	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Risk factors for & patient outcomes associated with ESBL-EC- and ESBL-Ks- bacteraemia, appropriateness of empiric antibiotic therapy & effect of inappropriate empiric therapy on outcomes	GNB
Denis B[68]	2005-2009	France	Case-control study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Prevalence & risk factors for ESBL-EC bacteraemia, impact on length of stay &30day mortality	EC
Chopra T[69]	2004-2009	USA	Case cohort study	Case 2(Control1): non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Predictors of ESBL-EC- and ESBL-KP-BSI, focus on cefepime exposure.	EC, KP
Panhotra BR[20]	2001-2003	Kingdom of Saudi Arabia	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors & clinical outcome of ESBL-KP-bacteraemia (hospital acquired)	KP
Marra AR[21]	1996-2001	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	ESBL-KP- associated mortality	KP
Skippen I[22]	2003-2005	UK	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-invasive transmission of organism in the healthcare setting	GNB
Schwaber MJ[23]	2000-2003	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Outcomes of ESBL-production in Enterobacteriaceae-bacteraemia.	GNB
Apisarnthanarak A[24]	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All adult patients	Entire hospital	All-cause mortality, LOS	Clinical & molecular epidemiologic factors associated with community onset ESBL-EC- infections, hospital resource utilisation, estimate costs associated with medical care (hospitalised patients)	EC
Tumbarello M[25]	1999-2003	Italy	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS, ICU-LOS	Factors associated with isolation of ESBL- KP-strains	KP
Zeistner R[11]	2008-2010	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital,	All-cause mortality, LOS	Difference in mortality: ESBL-EC-BSIs vs. non-ESBL-EC-BSIs, molecular epidemiology of ESBL-positive isolates	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Apisarnthanarak A[26]	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-infections (healthcare associated)	EC, KP
Kanafani ZA[27]	2003	Lebanon	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Epidemiology of infections with ESBL-EC and ESBL-Ks at AUBMC risk factors & outcomes of infections - focus on effect of prior antibiotic administration & the risks imparted by specific classes of antimicrobial agents	GNB
Zaoutis TE[28]	1999-2003	USA	Case cohort study	Non-ESBL-infection	Children	Entire hospital	All-cause mortality, LOS	Risk factors & outcomes associated with ESBL-EC-and ESBL-KP-BSI	EC, KP
Loh LC[29]	2003-2004	Malaysia	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Impact of ESBL-KP-respiratory tract infections on hospital mortality, requirement for mechanical ventilation & length stay	KP
Melzer M[30]	2003-2005	UK	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Differences in mortality & length of hospital stay &time from bacteraemia to death in patients with ESBL-EC- vs. non-ESBL-EC-bacteremic-infection	EC
Song KH[31]	2000-2006	South Korea	Case cohort study	Non-ESBL-infection	Patients with spontaneous bacterial peritonitis	Not provided	All-cause mortality (28 day)	Outcomes of ESBL-EC-and ESBL-Ks- vs non-ESBL-EC-and ESBL-Ks-SBP (based on isolation from ascites), impact of ineffective initial antimicrobial therapy on outcome in patients with ESBL-EC- and ESBL-Ks-SBP, risk factors for infection by ESBL-producing microorganisms.	GNB
Bennett JW[32]	2004-2008	USA	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU, Surgical ward, Burn unit	All-cause mortality (28 day)	ESBL types and strain variability, presence of host factors to determine potential role in morbidity and mortality during ESBL-KP-infections	KP
Trecarichi EM[33]	2000-2007	Italy	Cohort study, retrospective	Non-ESBL-infection	Patients with hematological malignancies	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality in patients suffering from hematological malignancies with concurrent EC-bacteraemia. Focus on impact of ESBL- production & fluoroquinolone resistance by bacterial isolates	EC
Tuon FF[34]	2006-2009	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Risk factors & mortality rate in ESBL-KP-bacteraemia	KP
Kang CI[35]	2008-2009	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors of ESBL-EC among community-onset bacteraemia, treatment outcomes	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Pena C[36]	1996-2003	Spain	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality among patients with EC- infections	EC
Tumbarello M[37]	2006	Italy	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	ICU, Medical ward, Entire hospital, surgical wide	All-cause mortality (21 day), LOS	Clinical &economic impacts of ESBL production, inadequate Initial Antibiotic Therapy of EC-BSI	EC
Kang CI[38]	2006-2009	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality (28 day)	Impact of ESBL-producing bacteraemia on outcome in patients with hematologic malignancy.	EC, KP
Wu YH[39]	2009-2012	Taiwan	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Medical ward	LOS	Host-related risk factors for community-onset UTI due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production, clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens	GNB
Rodriguez-Bano J[40]	2004-2006	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Epidemiology& risk factors (focus on previous antimicrobial use) & mortality rate for patients with ESBL-EC-COBSI	EC
Gürtnke S[41]	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Distribution of ESBL genotypes, hospital mortality in cases of ESBL-KP-BSI	KP
Oh MM[42]	2006-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients after Prostatitis Biopsy	Entire hospital	LOS	Impact of ESBL-positive-strains on clinical course & progression to chronic prostatitis in patients with postbiopsy acute prostatitis.	GNB
Leistner R[43]	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Financial disease burden attributable to ESBL-positive species in cases of EC-and KP-BSI	EC, KP
Lin JN[12]	2005-2009	Taiwan	Case cohort study	Non-ESBL-infection	All kinds of patients	Emergency Room	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Clinical & microbiological characteristics, risk factors for acquisition of infection, prescription of initial empirical antibiotics mortality rate of infection	GNB
Su NS[44]	2006-2010	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Clinical usefulness of breakpoints for treatment of Enterobacteriaceae-bacteraemia, (focus on EC- and Ks-bacteraemia): CLSI 2009- vs. CLSI 2010-guidelines.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Anunnatsiri S[45]	2005-2006	Thailand	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Incidence of ESBL-EC-septicemia, factors associated with infection & clinical outcomes	EC
Kang CI[46]	1998-2002	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Hospital-wide	All-cause mortality (28 day)	Risk factors for mortality & treatment outcome of ESBL-EC- and ESBL-KP-BSI	EC, KP
Raviv Y[47]	2004-2007	Israel	Cohort study, retrospective	Control group: non-ESBL-infection, second control group: no infection	patients with lung transplantation	Not provided	All-cause mortality (28 day)	Outcomes of lung transplant recipients infected by CRKP and ESBL carbapenem-sensitive KP (referred to MDR-KP)	KP
Kim HJ[13]	2005-2010	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Medical ward	All-cause mortality (28 day), LOS	Clinical outcome of patients with biliary tract infection: ESBL-producing bacterial isolates vs. non-ESBL-producing-bacterial isolates, predictors of poor prognosis, impact of ineffective antimicrobial therapy on clinical outcome	EC, KP
MacVane SH[48]	2011-2012	USA	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	clinical & economic outcomes of patients with ESBL-EC- and ESBL-KP-UTI vs. non-ESBL-EC- and non-ESBL-KP-UTI	EC, KP
Abhilash KP[49]	2007	India	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Prevalence & risk factors & outcome of antibiotic treatment among hospitalised patients with ESBL-EC- and ESBL-Ks-BSI	GNB
Shanthi M[50]	2006	India	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Prevalence & impact on clinical outcome of ESBL-production among nosocomial isolates of EC & KP	EC, KP
Han SB[51]	2009-2013	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children (immunocompromised, with cancer, neutropenic fever)	Pediatric ward	Attributable mortality, all-cause mortality (28 day)	Clinical outcomes of ESBL-EC- and ESBL-KP-bacteraemia & their antibiotic susceptibilities	EC, KP
Lee S[52]	2009-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with Acute Pyelonephritis	Entire hospital	All-cause mortality (14 day), LOS	Impact of ESBL on clinical outcomes of Acute Pyelonephritis treated with empirical ceftriaxone (which was inappropriate for ESBL-producing organisms)	EC
Artero A[70]	2013-2015	Spain	Cohort study, prospective	Non-ESBL-infection	Elderly	Medical ward	All-cause mortality, LOS	Identify clinical factors to predict ESBL-EC among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-EC	EC

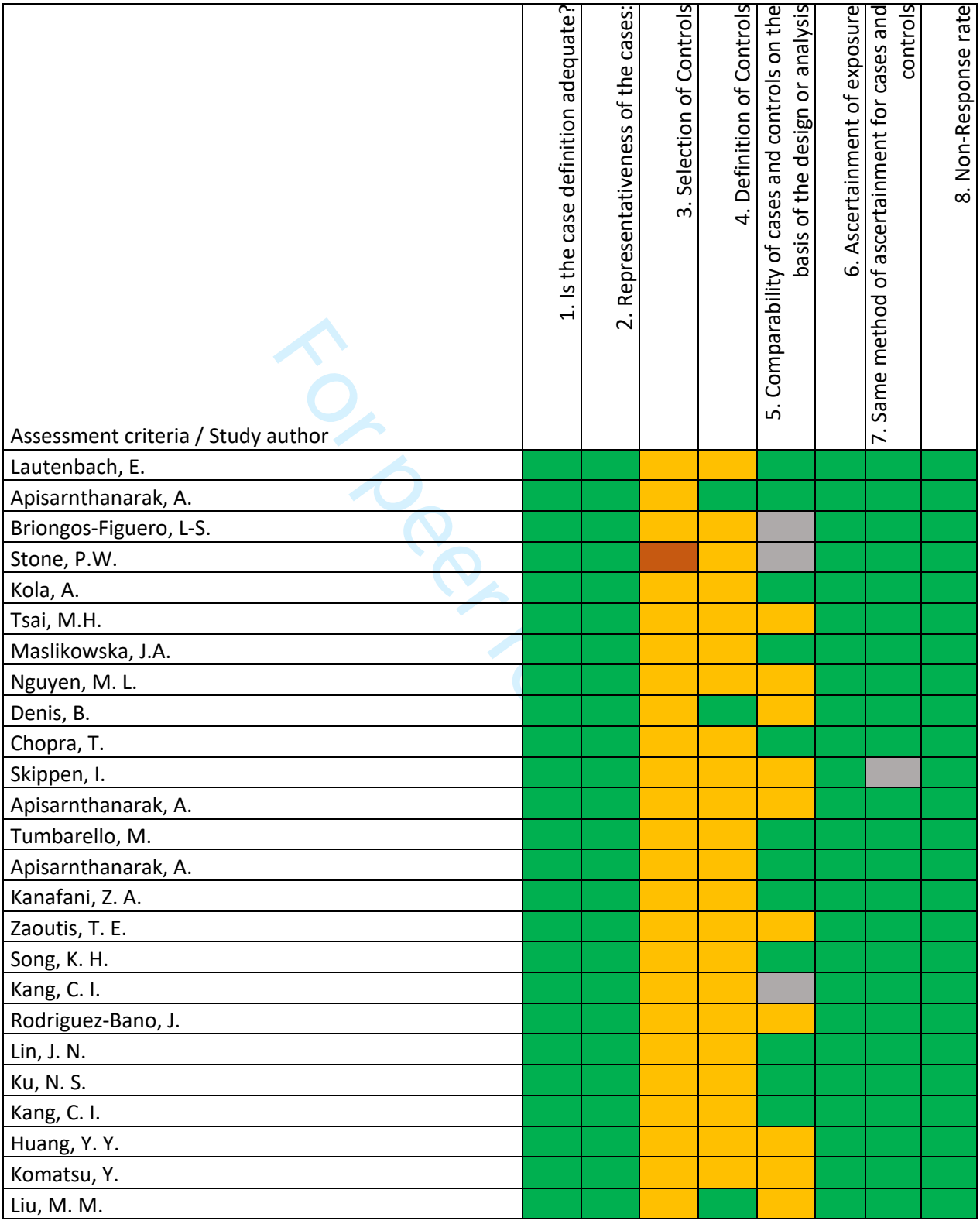
	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Chen IL[71]	2004-2015	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Compare the clinical characteristics & laboratory data of preterm babies with EC BSI: survival vs. nonsurvival groups, ESBL vs non-ESBL groups, determine the predictive factors of EC BSI in preterm babies	EC
Islas-Munoz B[72]	2016-2017	Mexico	Cohort study, prospective	Non-ESBL-infection	Cancer patients	Oncological ward	All-cause mortality (28 day)	Evaluate the clinical epidemiological characteristics & risk factors associated with mortality in cancer patients with BSI-special emphasis on MDR bacteria	GNB (and others)
Ma J[73]	2012-2015		Cohort study, retrospective	Non-ESBL-infection	Patients with hematological diseases	Entire hospital	All-cause mortality (28 day)	Evaluate the antimicrobial resistance & clinical features & risk factors for septic shock & death of nosocomial EC-BSI	EC
Man MY[74]	2009-2016	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients, except patients from Burn unit, transplant surgery ward or with thoracic therapy	Entire hospital	All-cause mortality (28 day)	Evaluate the incidence & clinical characteristics & outcomes of patients with KP BSI in critical care & general ward settings	KP
Marando R[75]	2016	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates	NICU	All-cause mortality	Investigate factors associated with ESBL-PE neonatal sepsis & mortality among neonates, characterise selected isolates to show virulence potential & transmission dynamics	GNB
Namikawa H[76]	2011-2015	Japan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate clinical characteristics of patients with ESBL-EC-BSI	EC
Shi SH[77]	2008-2015	China	Cohort study, retrospective	Non-ESBL-infection	Patients with pyogenic liver abscess	Centre for hepatopancreaticobiliary diseases	All-cause mortality, LOS	Aetiology & morbidity & clinical characteristics of pyogenic liver abscess caused by ESBL-PE	GN
Tanir Basaranoglu S[78]	2011-2015	Turkey	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	Assess risk factors for health care associated ESBL-KP-BSI in children, analyze clinical outcomes: ESBL-KP vs. non-ESBL-KP	KP
Razazi K[79]	2009-2015	France	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality, LOS, ICU-LOS	Determine, among ESBL-PE carriers, the prevalence & associated factors & clinical impact of ESBL-PE pneumonia, determine factors associated with ICUAP caused by carbapenem-resistant bacteria	GNB

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Ray S[80]	2014-2016	India	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Investigate spectrum of microbial resistance pattern in the community and their effects on mortality	GNB
Haruki Y[81]	2006-2016	Japan	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Compare the clinical characteristics & outcomes of critically ill patients in an ICU, who were hospitalised for BSI caused by ESBL-EC or non-ESBL-EC.	GNB
Lin WT[82]	2009-2014	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate the clinical manifestations & bacteriological features of culture-proven, GNB arthritis	GNB
Buys H[83]	2006-2011	South Africa	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Describe the clinical presentation of KPBSI, risk factors associated with ESBL-KPBSI, antibiotic susceptibility patterns of the KP isolates & KPBSI mortality including factors associated with in-patient mortality	KP
Lee CC[84]	2008-2013	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Emergency Department	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Analyse the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics & bacteraemia severity by using a propensity-matched analysis (PSM)	GNB
Huang YY[85]	2011-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Determine cumulative incidence of ESBL urosepsis, identify major risk factors for ESBL urosepsis, determine impact of international travel on development of ESBL urosepsis	EC, KP
Komatsu Y[86]	2008-2013	Japan	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Identify risk factors & clinical outcomes in patients with BSI due to ESBL- or carbapenemase-producing EC, determine prevalence & genetic background	EC
Liu MM[87]	2011-2016	China	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	ICU-patients	ICU	All-cause mortality	Identify risk factors for ESBL-producing ECBSI among carriers at ICU	EC
Nivesvivat T[88]	2010-2017	Thailand	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality, LOS	Determine prevalence, risk factors & clinical outcomes of ESBL-producing EB in paediatric BSI	EC, KP

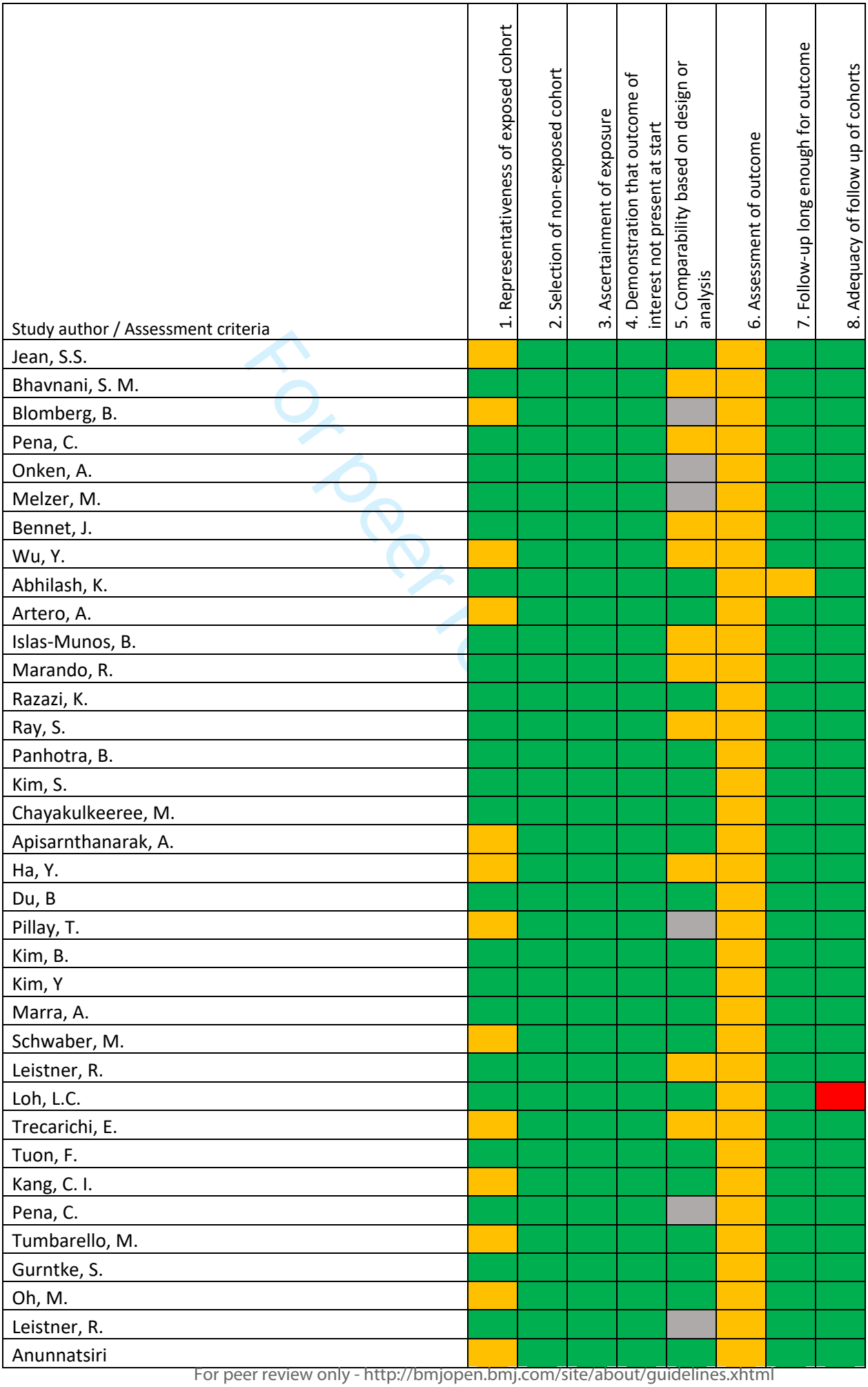
	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Cordery RJ[89]	2004-2006	UK	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Elucidate specific risk factors for the acquisition of ESBL infection in the ICU; all-cause mortality (in ICU) compared in patients with infections due to ESBL- and non-ESBL-producing organisms	GNB
Paikos GL[90]	2003-2005	Greece	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Identify risk factors associated BSI caused by integron-carrying EB; evaluate the consequences of these genetic elements on patient outcome	GNB
Gudiol C[91]	2006-2008	Spain	Cohort study, prospective	Non-ESBL-infection	Cancer patients and hematopoietic stem cell transplant patients	Entire hospital	All-cause mortality	Assess clinical features, risk factors, molecular epidemiology & outcome of ESBLEC BSI in hospitalised cancer patients	EC
Marchaim D[92]	2006-2008	Israel	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Define predictors & outcomes of ESBL BSI among patients with bacteraemia due to EB upon hospital admission	GNB
Menashe G[93]	1997	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Determine: prevalence of ESBL-P organisms among adult patients with nosocomial EB BSI treated in our institution; association between ESBL production & resistance to other antibiotics; clinical characteristics of patients with nosocomial ESBL-P BSI compared with those infected with non-producing strains; impact of ESBL production on outcome of patients with nosocomial EB BSI	GNB
Ortega M[94]	1991-2007	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Describe source, resistance rate to fluoroquinolone & beta-lactam antibiotics and mortality of EC BSI episodes in a single institution; identify predictive factors for isolation of fluoroquinolone-resistant or ESBL- producing strains.	EC
Szilgyi M[95]	2005-2008	Hungary	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality,	Investigate risk factors for & outcomes of BSI caused by ESBL-producing and ESBL-non-producing KP	KP
Tsai SS[96]	2005-2006	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Diabetic patients	Entire hospital	All-cause mortality	Analyze characteristics, risk factors & outcomes of diabetic patients with community- vs. hospital-acquired KP BSI	KP

EC = *Escherichia coli*
KP = *Klebsiella pneumoniae*
GNB = Gram-negative bacteria
BSI = Bloodstream infection
UTI = Urinary tract infection
ICU = Intensive care unit
NICU = Neonatal intensive care unit
ESBL-PE = Extended-spectrum beta-lactamase-producing Enterobacteriaceae
EB = Enterobacteriaceae
LOS = Length of stay

Supplementary table S5: Risk of bias assessment of case cohort studies according to Newcastle - Ottawa quality assessment scale:



Risk of bias assessment of cohort studies according to Newcastle - Ottawa quality assessment scale:



Raviv, Y.								
Kim, H.J.								
MacVane, S.								
Shanthi								
Han, S.B.								
Lee, S.								
Chen, I-L.								
Ma, J.								
Man, M.								
Namikawa, H.								
Shi, S.								
Tanir Basarangolu, S.								
Haruki, Y.								
Lin, W.								
Buys, H.								
Lee, C.C.								
Nivesvivat, T.								

Supplementary table S6: Source of heterogeneity among effect estimates in studies on ESBL bloodstream infections in comparison with patients with non-ESBL bloodstream infections assessed using univariate meta-regression:

Subgroups / Outcome	All-cause mortality	Length of Stay
Mortality time	0.85	-
Pathogen	0.45	0.34
Study design	0.51	0.21
Study country	0.22	0.09
Income classification	0.17	0.80
Study period	0.57	0.78
Study setting: ICU ward	0.78	0.97
Study setting: Neonatal ward	0.62	0.97
Study setting: Pediatric ward	0.96	0.96
Study population: ICU patients	1.00	-
Study population: Children	0.96	0.96
Study population: Neonates	0.62	0.97
Information about therapy	0.53	
Appropriatness of therapy reported	0.68	
Information about outcome of therapy	0.74	-
MIC reported	0.28	-

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	suppl.material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 and suppl. material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	suppl.material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 and suppl. material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

For more information, visit: **www.prisma-statement.org**.